IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH,	)	
	)	
Plaintiff,	)	
	)	C. A. No. 06-222 (JJF)
v.	)	
	)	**REDACTED -**
IMPAX LABORATORIES, INC.,	)	**PUBLIC VERSION**
	)	
Defendant.	)	

VOLUME IV OF IV (EXHIBITS 30-67) TO THE CONSOLIDATED DECLARATION OF KAREN JACOBS LOUDEN IN SUPPORT OF WYETH'S COUNTERSTATEMENTS IN OPPOSITION TO IMPAX'S MOTIONS FOR SUMMARY JUDGMENT

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH,	)	
Plaintiff,	)	C. A. No. 06-222 (JJF)
v.	)	
IMPAX LABORATORIES, INC.,	)	**REDACTED – PUBLIC VERSION**
Defendant.	)	

CONSOLIDATED DECLARATION OF KAREN JACOBS LOUDEN IN SUPPORT OF WYETH'S COUNTERSTATEMENTS IN OPPOSITION TO IMPAX'S MOTIONS FOR SUMMARY JUDGMENT

I, Karen Jacobs Louden, hereby declare as follows:

1. I am a partner with the law firm of Morris, Nichols, Arsht & Tunnell, LLP. I am one of the attorneys representing Wyeth in the current litigation.

2. Attached hereto as Exhibit 1 is a true and correct copy [redacted]

3. Attached hereto as Exhibit 2 is a true and correct copy [redacted].

4. Attached hereto as Exhibit 3 is a true and correct copy [redacted]

5. Attached hereto as Exhibit 4 is a true and correct copy [redacted]

6. Attached hereto as Exhibit 5 is a true and correct copy [redacted]

7. Attached hereto as Exhibit 6 is a true and correct copy [redacted]

8. Attached hereto as Exhibit 7 is a true and correct copy [redacted]

9. Attached hereto as Exhibit 8 is a true and correct copy [redacted]

10. Attached hereto as Exhibit 9 is a true and correct copy [redacted]

11. Attached hereto as Exhibit 10 is a true and correct copy [redacted]

12. Attached hereto as Exhibit 11 is a true and correct copy [redacted]

13. Attached hereto as Exhibit 12 is a true and correct copy [redacted]

14. Attached hereto as Exhibit 13 is a true and correct copy [redacted]

15. Attached hereto as Exhibit 14 is a true and correct copy [redacted]

16. Attached hereto as Exhibit 15 is a true and correct copy [redacted]

17. Attached hereto as Exhibit 16 is a true and correct copy [redacted]

18. Attached hereto as Exhibit 17 is a true and correct copy [redacted]

19. Attached hereto as Exhibit 18 is a true and correct copy [redacted]

20. Attached hereto as Exhibit 19 is a true and correct copy [redacted]

21. Attached hereto as Exhibit 20 is a true and correct copy [redacted]

22. Attached hereto as Exhibit 21 is a true and correct copy of a document bearing Bates Numbers WYETH208-000072 to 000095.

23. Attached hereto as Exhibit 22 is a true and correct copy [redacted]

24. Attached hereto as Exhibit 23 is a true and correct copy [redacted]

25. Attached hereto as Exhibit 24 is a true and correct copy [redacted]

26. Attached hereto as Exhibit 25 is a true and correct copy [redacted]

27. Attached hereto as Exhibit 26 is a true and correct copy [redacted]

28. Attached hereto as Exhibit 27 is a true and correct copy [redacted]

29. Attached hereto as Exhibit 28 is a true and correct copy [redacted]

30. Attached hereto as Exhibit 29 is a true and correct copy [redacted]

31. Attached hereto as Exhibit 30 is a true and correct copy [redacted]

32. Attached hereto as Exhibit 31 is a true and correct copy [redacted]

33. Attached hereto as Exhibit 32 is a true and correct copy [redacted]

34. Attached hereto as Exhibit 33 is a true and correct copy [redacted]

35. Attached hereto as Exhibit 34 is a true and correct copy [redacted]

36. Attached hereto as Exhibit 35 is a true and correct copy [redacted]

37. Attached hereto as Exhibit 36 is a true and correct copy [redacted]

38. Attached hereto as Exhibit 37 is a true and correct copy [redacted]

39. Attached hereto as Exhibit 38 is a true and correct copy [redacted]

40. Attached hereto as Exhibit 39 is a true and correct copy of the Assignment Transferring Rights to U.S. Patent No. 5,506,270 from Upton, Derivan, and Rudolph to American Home Products Corporation.

41. Attached hereto as Exhibit 40 is a true and correct copy of an article entitled J. Russell, *Relatively Low Doses of Cisapride in the Treatment of Nausea in Patients Treated with Venlafaxine for Treatment-Refactory Depression*, J. Clin. Psychopharmacology, Vol. 16, No. 1, pp. 35-37 (1996).

42. Attached hereto as Exhibit 41 is a true and correct copy of [redacted]

43. Attached hereto as Exhibit 42 is a true and correct copy of the Assignment Transferring Rights for the Patents-in-Suit from S. White to American Home Products Corporation.

44. Attached hereto as Exhibit 43 is a true and correct copy [redacted]

45. Attached hereto as Exhibit 44 is a true and correct copy [redacted]

46. Attached hereto as Exhibit 45 is a true and correct copy [redacted]

47. Attached hereto as Exhibit 46 is a true and correct copy [redacted]

48. Attached hereto as Exhibit 47 is a true and correct copy [redacted]

49. Attached hereto as Exhibit 48 is a true and correct copy [redacted]

50. Attached hereto as Exhibit 49 is a true and correct copy of excerpted pages from the 19th Edition of *Remington: The Science and Practice of Pharmacy*, (1995) Vol. II, Ch. 92.

51. Attached hereto as Exhibit 50 is a true and correct copy of [redacted]

52. Attached hereto as Exhibit 51 is a true and correct copy of an article entitled Sarkar, "*Thermal Gelation Properties of Methyl and Hydroxypropyl Methylcellulose [i.e., HPMC]*", Journal of Applied Polymer Science, Vol. 24, pp. 1073-1087 (1979).

53. Attached hereto as Exhibit 52 is a true and correct copy [redacted]

54. Attached hereto as Exhibit 53 is a true and correct copy [redacted]

55. Attached hereto as Exhibit 54 is a true and correct copy [redacted]

56. Attached hereto as Exhibit 55 is a true and correct copy [redacted]

57. Attached hereto as Exhibit 56 is a true and correct copy of excerpted pages from the Handbook of Pharmaceutical Excipients: Microcrystalline Cellulose, edited by R. C. Rowe et al., pp. 108-111 (4th ed. 2003).

58. Attached hereto as Exhibit 57 is a true and correct copy of excerpted pages from the Handbook of Pharmaceutical Excipients: Sugar Spheres, edited by R.C. Rowe et al., pp.630-631 (4th ed. 2003).

59. Attached hereto as Exhibit 58 is a true and correct copy of excerpted pages from the Handbook of Pharmaceutical Excipients: Povidone, edited by R.C. Rowe et al., pp.508-513 (4th ed. 2003).

60. Attached hereto as Exhibit 59 is a true and correct copy [redacted]

61. Attached hereto as Exhibit 60 is a true and correct copy [redacted]

62. Attached hereto as Exhibit 61 is a true and correct copy of U.S. Patent No. 5,885,616, issued on March 23, 1999.

63. Attached hereto as Exhibit 62 is a true and correct copy [redacted]

64. Attached hereto as Exhibit 63 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 08/821,137.

65. Attached hereto as Exhibit 64 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 08/964,328.

66. Attached hereto as Exhibit 65 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 09/488,629.

67. Attached hereto as Exhibit 66 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 09/884,412.

68. Attached hereto as Exhibit 67 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 09/950,965.

I declare under penalty of perjury that the foregoing is true and correct, and that this declaration was executed on this 28th day of December, 2007.

/s/ Karen Jacobs Louden (#2881)
Karen Jacobs Louden (#2881)

1347978

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on January 8, 2008, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

Mary B. Matterer
MORRIS JAMES LLP

I also certify that copies were caused to be served on January 8, 2008 upon the following in the manner indicated:

BY E-MAIL AND HAND

Mary B. Matterer
MORRIS JAMES LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19899

BY E-MAIL

Joseph C. Gratz
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KEKER & VAN NEST LLP
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San Francisco, CA 94111-1704

/s/ Karen Jacobs Louden

Karen Jacobs Louden (#2881)
klouden@mnat.com

Exhibit 30

REDACTED

Exhibit 31

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Exhibit 32

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Exhibit 33

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Exhibit 34

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Exhibit 35

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Exhibit 36

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Exhibit 37

REDACTED

Exhibit 38

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Exhibit 39

A 1327093

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 02, 2005

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON NOVEMBER 20, 1995

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WILLIAMS
Certifying Officer

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OMB No. 0651-0011 (exp. 4/94)

RECOR

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Patent and Trademark Office

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To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Gertrude V. Upton
Albert T. Derivan
Richard L. Rudolph

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: American Home Products Corporation

Internal Address:

Street Address: Five Giralda Farms

City: Madison State: NJ ZIP: 07940

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other

Execution Date: Jan. 24 & 30, 1995

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
08/380,903
Filed: January 30, 1995

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Ronald W. Alice-American Home Products Corporation

Internal Address:

Street Address: Five Giralda Farms

City: Madison State: NJ ZIP: 07940

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00

☐ Enclosed

☒ Authorized to be charged to deposit account

8. Deposit account number:

01-1425

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Ronald W. Alice
Name of Person Signing

Signature

11/15/95
Date

Total number of pages including cover sheet, attachments, and document: 5

Mail documents to be recorded with required cover sheet information to:
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Washington, D.C. 20231

PATENT
REEL: 7738 FRAME: 0730

AHP-94139
PATENT

SERIAL NO. 380,903

FILED: January 30, 1995

ASSIGNMENT

WHEREAS, we:

(1) Gertrude V. Upton

(2) Albert T. Derivan

(3) Richard L. Rudolph

residing, respectively, at:

	TOWN OR CITY:	IN THE COUNTY OF:	AND IN THE STATE OF:
(1)	Radnor	Delaware	Pennsylvania
(2)	Villanova	Delaware	Pennsylvania
(3)	Berwyn	Chester	Pennsylvania

have invented certain new and useful Improvements in

VENLAFAXINE IN THE TREATMENT OF HYPOTHALAMIC AMENORRHEA IN NON-DEPRESSED WOMEN

for which we have, respectively, on:

(1) the 20th day of January, 1995

(2) the 30 day of January, 1995

(3) the 24th day of January, 1995

executed an application for Letters Patent of the United States, the date of filing and serial number of said application, when known to be inserted above; and

WHEREAS, AMERICAN HOME PRODUCTS CORPORATION, a corporation duly organized and existing under the laws of the State of Delaware, and having a place of business at Five Giralda Farms, in the County of Morris, and State of New Jersey, hereinafter called ASSIGNEE, is desirous of acquiring the entire right, title and interest in and to said invention, in the United States of America, its territories, dependencies and possessions, and in all foreign countries, and in and to any United States or foreign Letters Patent that may be granted therefor, and in and to such other forms of protection of industrial property as may be granted therefor pursuant to the laws of any country:

NOW, THEREFORE, in consideration of ONE DOLLAR ($1.00) in hand paid to each of us, and other good and valuable considerations, the receipt of which is hereby acknowledged, we by these presents, have sold, assigned and transferred, and do hereby sell, assign and transfer, to ASSIGNEE, its successors, legal representatives

and assigns, the entire right, title and interest in and to the said invention, in the United States of America, its territories, dependencies and possessions, and in all foreign countries, and in and to any Letters Patent of the United States and foreign countries (including all divisions, reissues, continuations and extensions thereof) that may be granted therefor, and in and to such other forms of protection of industrial property as may be granted therefor pursuant to the laws of any country, and the right to apply for Letters Patent and such other forms of protection of industrial property as may be provided by any country, with full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty or by international convention, together with the right to extend the protection of said United States Letters Patent to territorial possessions now owned or which may hereafter be acquired by the United States of America, for the full term for which said Letters Patent or said other forms of protection may be granted;

And we covenant and agree with ASSIGNEE that we have a full and unencumbered title to the invention hereby assigned, which title we warrant to ASSIGNEE;

And we further agree that we will, at ASSIGNEE'S request, without demanding further consideration therefor but entirely at ASSIGNEE'S expense, do all lawful and just acts, including the execution and acknowledgement of instruments, that may be or become necessary for obtaining, sustaining or reissuing United States and foreign Letters Patent or said other forms of protection covering the invention hereby assigned, and for maintaining and perfecting ASSIGNEE's right to said invention, Letters Patent and other forms of protection, particularly in cases of interference and litigation.

IN WITNESS WHEREOF, we have respectively, hereunto set our hands and seals:

(1) this 24 day of January, 1995

(2) this 30 day of January, 1995

(3) this 24th day of January, 1995

(1) Gertrude V. Upton (L.S.)
Gertrude V. Upton

WITNESS AS TO (1):

AHP-94139
PATENT

(2) _____ (L.S.)
Albert T. Derivan

WITNESS AS TO (2):

_____

_____

(3) _____ (L.S.)
Richard L. Rudolph

WITNESS AS TO (3):

_____

_____

STATE OF PENNSYLVANIA)
: SS:
COUNTY OF DELAWARE)

On this 24th day of January, 1995, before me personally appeared

(1) Gertrude V. Upton

to me known and known to me to be the individual described in and who executed the foregoing instrument, and she acknowledged to me that she executed the same.

_____
Notary Public

NOTARIAL SEAL
ROXANNE L. KELLY, Notary Public
Radnor Twp., Delaware Co.
My Commission Expires Nov. 23, 1998

STATE OF PENNSYLVANIA)
: SS:
COUNTY OF DELAWARE)

On this 30th day of January, 1995, before me personally appeared

(2) Albert T. Derivan

to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same.

Roxanne L. Kelly
Notary Public

NOTARIAL SEAL
ROXANNE L. KELLY, Notary Public
Radnor Twp., Delaware Co.
My Commission Expires Nov. 23, 1998

STATE OF PENNSYLVANIA)
: SS:
COUNTY OF DELAWARE)

On this 24th day of January, 1995, before me personally appeared

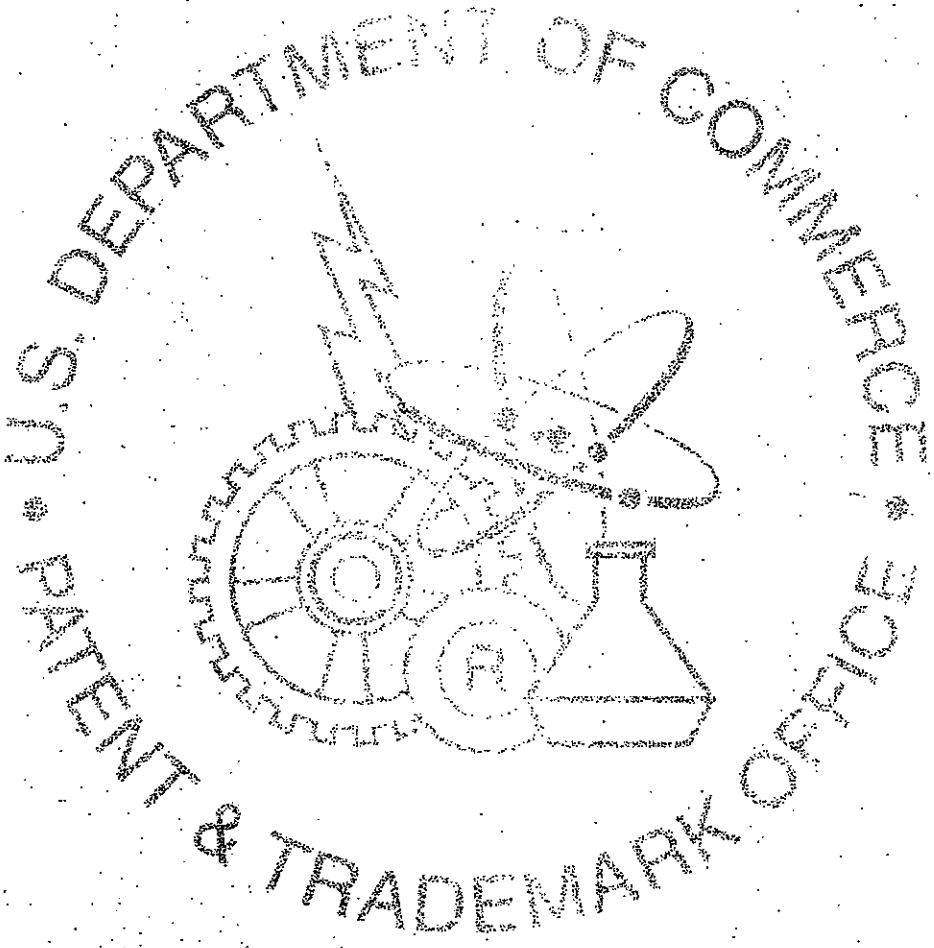
(3) Richard L. Rudolph

to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same.

Roxanne L. Kelly
Notary Public

NOTARIAL SEAL
ROXANNE L. KELLY, Notary Public
Radnor Twp., Delaware Co.
My Commission Expires Nov. 23, 1998

RECORDED: 11/20/1995 PATENT REEL: 7739 FRAME: 0734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UNITED STATES PATENT & TRADEMARK OFFICE

Exhibit 40

0271-0749/96/1601-0035$03.00/0
Journal of Clinical Psychopharmacology

Vol. 16, No. 1
Printed in U.S.A.

Relatively Low Doses of Cisapride in the Treatment of Nausea in Patients Treated With Venlafaxine for Treatment-Refractory Depression

JOHNNA L. RUSSELL, MD

University of Mississippi Medical Center, Department of Psychiatry and Human Behavior, Jackson, Mississippi

Low doses of cisapride (5–10 mg twice daily) produced relatively rapid relief from nausea elicited by venlafaxine in six patients with treatment-refractory recurrent major depression. This further suggests that the nausea associated with serotonergic reuptake inhibition may be a result of 5-hydroxytryptamine (5-HT_3) agonist action. No adverse cardiac experiences were encountered in spite of the potential interaction of cisapride with selective serotonin reuptake inhibitors at the cytochrome P4503A4 enzyme system. (J Clin Psychopharmacol 1996;16:35–37)

VENLAFAXINE IS A novel antidepressant with both serotonergic and noradrenergic reuptake inhibitory activity.[1] It was recently released in the United States for treatment of major depression; however, its generalized use as an agent of first choice has been limited by the incidence of nausea associated with administration of the drug. Even when company manufacturer's suggestions are followed and the drug is started at low dosage and taken with meals, as many as one third of the patients experience significant nausea, and, of these, as many as 50% discontinue the drug because of this side effect.[2]

Nausea and gastrointestinal side effects have been a problem with several drugs possessing reuptake inhibition of serotonin. Theoretically, these reuptake inhibitors have the ability to activate all subtypes of 5-hydroxytryptamine (5-HT) receptors. 5-HT_3 antagonists have been used to attenuate the nausea and emesis in patients who are undergoing chemotherapy.[3] Therefore, it is possible to postulate that the nausea produced by venlafaxine might be etiologically related to the activation of 5-HT_3 receptors.[4] There is a selective 5-HT_3 antagonist commercially available (ondansetron), but it is expensive, has a short half-life (3 hours), and must be given parenterally. Its use is impractical for the treatment of nausea produced by venlafaxine. Blier and Bouchard[5, 6] have shown that the substituted benzaprides, zacopride and cisapride, block the enhancement of the electrically evoked release of tritiated 5-HT produced by 5-HT_3 agonists in guinea pigs. In blocking 5-HT receptors, benzamides probably act like 5-HT_3 antagonists such as ondansetron.

Cisapride was recently introduced into the U.S. market as an oral gastric reflux agent that induces rapid gastric emptying and is relatively inexpensive when compared with ondansetron. Previously futile attempts to treat the nausea associated with venlafaxine with metoclopramide, promethazine hydrochloride, and prochlorperazine as well as the relative inexpensiveness of cisapride resulted in its choice as a potential antinauseant to counteract this side effect of venlafaxine.

Method

Six patients were given a diagnosis of major depression, recurrent, according to the diagnostic criteria in the *Diagnostic and Statistical Manual*, fourth edition (DSM-IV). The patients were assigned as class 3 treatment refractory according to the classification system proposed by Thase and colleagues[7] (having failed to respond to adequate trials of at least two classes of dissimilar antidepressants and at least one augmentation strategy). Interestingly, none of these patients had had any significant difficulty with nausea on previous antidepressant regimens. All six patients were administered oral venlafaxine, 25 mg twice daily. These six patients were selected because of their similar diagnosis, relative freedom from other medical problems, and their substantial complaints of nausea within 48 hours after taking the initial dose of venlafaxine. All patients were then administered oral cisapride, 5 mg twice daily, as an addition to their venlafaxine regimen. They continued to take the venlafaxine orally, with meals, and,

Received November 4, 1994, and accepted June 29, 1995.
Address requests for reprints to: Johnna L. Russell, MD, University of Mississippi Medical Center, Department of Psychiatry and Human Behavior, 2500 North State Street, Jackson, MI 39216-4505.

by the third week, were on regimens of at least 75 mg twice daily. In two cases, the cisapride was increased to 10 mg, orally, twice daily because of continued nausea. The resolution of the nausea was then evaluated as either a marked relief of nausea or a disappearance of nausea on the basis of patient report.

Results

In these six patients with treatment-refractory major depression, nausea began within the first 2 days of administration of venlafaxine. In all patients, the nausea occurred on the lowest possible dose of venlafaxine, each patient taking the medication with meals. In four of the six patients, nausea was also associated with vomiting. The vomiting gradually disappeared in a maximum of 72 hours after cisapride administration in two of four patients. For the other two patients, an increased dosage of oral cisapride to 10 mg twice daily was required. In these two patients, the cisapride was interrupted for 1 day because the patients thought that the cisapride might have been contributing to the nausea and vomiting. However, the nausea and vomiting significantly worsened when they were taken off the cisapride; these symptoms were relieved when both patients were restarted on cisapride at double the original dose. The patients were maintained on cisapride once their nausea appeared to be in remission. The cisapride was then gradually tapered over 1 month without reappearance of the nausea. Total maximum time of cisapride treatment was 5 weeks. Final dosages of venlafaxine required for each patient are noted in Table 1. All patients had remission of their depression using venlafaxine at the final dosages as noted in Table 1.

Discussion

Much attention has been given to the potential for blood pressure increases with the new serotonergic/noradrenergic reuptake inhibitor venlafaxine. In clinical practice, venlafaxine has, instead, caused significant incidences of nausea and vomiting, which has limited its utility as a first-line antidepressant agent. For this reason, the patients reported here are all patients who had previously tried at least two different classes of antidepressants with at least one augmentation strategy. Manufacturers of venlafaxine have been quite aware of the potential of this drug to cause nausea and have made suggestions including reducing dosages, taking the drug with meals, and starting with low doses.[2] In all six patients, the lowest possible dosage was used from the outset, and the drug was taken with meals in an attempt to minimize the nausea. All six patients related that they wished to discontinue the drug secondary to nausea and/or vomiting. Of significance, in all six patients, cisapride successfully eliminated nausea after a maximum of 6 days. Also of importance, in two patients who discontinued cisapride because they thought that it was contributing to their nausea, nausea actually worsened and was later relieved by a higher dose of cisapride. A regimen of 5 to 10 mg of cisapride twice a day would be subtherapeutic for most individuals who would receive the drug for reflux or other gastrointestinal disorders. At larger doses, it is thought that cisapride acts by means of 5-HT receptor antagonism. It is thus possible that cisapride exerts its antiemetic effects as a 5-HT_3 antagonist. A similar hypothesis was recently proposed by Bergeron and Blier,[8] who used cisapride to treat the nausea associated with the administration of selective serotonin reuptake inhibitors (SSRIs) in a mix of patients with both premenstrual syndrome and depression.

In conclusion, these very preliminary results would seem to bolster the usefulness of cisapride treatment for nausea in patients who are taking venlafaxine as well as to support the hypothesis of Bergeron and Blier[8] that the efficacy of cisapride is probably related to its serotonergic 5-HT_3 antagonism. A note of caution in using cisapride is that it has been reported to cause tachycardia[9] as well as torsade de pointes in two patients who used cisapride in combination with ketoconazole.[10] However, ketoconazole competitively inhibits

TABLE 1. Patient characteristics and response to cisapride (5–10 mg twice daily) in patients with treatment-refractory major depression successfully treated with venlafaxine

Patient	Age	Sex	Dosage of Cisapride (mg/day)	Onset of Nausea (Days) After Beginning 25 mg Venlafaxine	Onset of Cisapride Action (Days)	Dosage of Venlafaxine at Time of Cisapride Discontinuation (mg/day) (All Subjects in Remission)
1	28	M	10	2	1	150
2	46	M	10	2	2	225
3	56	F	10	1	2	200
4	60	F	10	1	1	200
5	38	F	10/20[a]	1	5	250
6	47	M	10/20[a]	2	6	300

[a]Patients discontinued cisapride but had increased nausea, which subsided when cisapride was resumed at a higher dose.

the cytochrome P4503A4 enzyme system,[10] whereas venlafaxine inhibits the cytochrome P4502D6 polymorphic enzyme.[11] Theoretically, there should be no cross-reaction at these enzyme systems; however, venlafaxine does interact with cimetidine, which also affects the P4503A4 enzyme. Certainly in this small set of patients, as well as those reported by Bergeron and Blier, cisapride has been of clinical utility in low doses to relieve the nausea secondary to venlafaxine and SSRI administration. Further investigation is needed not only to confirm the clinical utility in a prospective study but also to ascertain whether the nausea is actually related to 5-HT_3 activation by drugs with the capability for serotonergic reuptake inhibition. In addition, although all six patients in this series responded to venlafaxine with a 1-month intake of cisapride, it would still be important to have longer follow-up to ensure that cisapride does not interfere with the clinical utility of this antidepressant. Finally, given the reports of cardiac arrhythmias, although theoretically there should be no interaction between the 2D6 and 3A4 cytochrome P450 enzyme systems, and that venlafaxine does interact to inhibit the metabolism of cimetidine, caution is warranted in further investigation and prescription of cisapride with not only venlafaxine but also sertraline and fluoxetine.[12]

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Clinical Psychopharmacology

JOURNAL OF
CLINICAL PSYCHOPHARMACOLOGY

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ASSIGNMENT

WHEREAS, I, Stephen A. White, residing in the town of Champlain, County of ~~United States of America~~ in the State of New York, along with Deborah M. Sherman, John C. Clark and John U. Lamer have invented certain new and useful Improvements in

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for which I have on the 29 day of March, 2001, executed an application for Letters Patent of the United States, the date of filing and serial number of said application, when known to be inserted above; and

WHEREAS, AMERICAN HOME PRODUCTS CORPORATION, a corporation duly organized and existing under the laws of the State of Delaware, and having a place of business at Five Giralda Farms, in the City of Madison, County of Morris, and State of New Jersey, hereinafter called ASSIGNEE, is desirous of acquiring the entire right, title and interest in and to said invention, in the United States of America, its territories, dependencies and possessions, and in all foreign countries, and in and to any United States or foreign Letters Patent that may be granted therefor, and in and to such other forms of protection of industrial property as may be granted therefor pursuant to the laws of any country:

NOW, THEREFORE, in consideration of ONE DOLLAR ($1.00) in hand paid to me, and other good and valuable considerations, the receipt of which is hereby acknowledged, I by these presents, have sold, assigned and transferred, and do hereby sell, assign and transfer, to ASSIGNEE, its successors, legal representatives and assigns, the entire right, title and interest in and to the said invention, in the United States of America, its territories, dependencies and possessions, and in all foreign countries, and in and to any Letters Patent of the United States and foreign countries (including all divisions, reissues, continuations and extensions thereof) that may be granted therefor, and in and to such other forms of protection of industrial property as may be granted therefor pursuant to the laws of any country, and the right to apply for Letters Patent and such other forms of protection of industrial property as may be provided by any country, with full benefit of such priorities as may now or hereafter be granted to me by local laws or by treaty or by international convention, together with the right to extend the protection of said United States Letters Patent to territorial possessions now owned or which may hereafter be acquired by the United States of America, for the full term for which said Letters Patent or said other forms of protection may be granted:

And I covenant and agree with ASSIGNEE that I have a full and unencumbered title to the invention hereby assigned, which title I warrant to ASSIGNEE;

And I further agree that I will, at ASSIGNEE's request, without demanding further consideration therefor but entirely at ASSIGNEE's expense, do all lawful and just acts, including the execution and acknowledgement of instruments, that may be or become necessary for obtaining, sustaining or reissuing United States and foreign Letters Patent or said other forms of protection covering the invention hereby assigned, and for maintaining and perfecting ASSIGNEE's right to said invention, Letters Patent and other forms of protection, particularly in cases of interference and litigation.

IN WITNESS WHEREOF, I have hereunto set my hand and seal this 29 day of March, 2001.

Stephen A. White (L.S.)

WITNESS:

Julie A. Winterbottom

Judy Lawyer

STATE OF NEW YORK)
:SS:
COUNTY OF CLINTON)

On this 29 day of March, 2001, before me personally appeared:

Stephen A. White

to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same.

Julie A. Winterbottom
Notary Public, State of New York
No. 01WI6023921
Qualified in Clinton County
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Julie A. Winterbottom
Notary Public

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rect compression. The method of preparation and the added ingredients are selected in order to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics and uniformity which also are influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets, the formulator also must be cognizant of the effect which the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet in order that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet, although containing the same quantity of drug substance, that gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[2,14,15] See Chapters 35, 42 and 83.

Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or *excipients*. They may be classified according to the part they play in the finished tablet. The first group contains those which help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders, glidants and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, colors, and in the case of chewable tablets, flavors and sweetening agents, and in the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

Although the term *inert* has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients*. This reference now is distributed widely throughout the world.[16]

Diluents

Frequently, the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets commonly are called *chewable tablets*. Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility. These are discussed under *Direct Compression*, page 1626.

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations. Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered, eg, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the gastrointestinal tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances, eg, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens. These drug substances may be adsorbed after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant, results in tablets which discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas. However, its presence in 5 to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation; eg, corn starch can be used in paste form as a binder. When added in drug or suspension form, it is a good disintegrant. Even though these two uses are to achieve opposite goals, some tablet formulas use corn starch in both ways. In some controlled-release formulas, the polymer hydroxypropylmethylcellulose (HPMC) is used both as an aid to prolong the release from the tablet, as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary in order to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum and larch arabogalactan. Other agents which may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies. Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically. Materials which have no cohesive qualities of their own will require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch and celluloses, they change the powdered material to granules and the residual moisture retained enables the materials to adhere together when compressed.

Binders are used both as a solution and in a dry form depending on the other ingredients in the formulation and the method of preparation. However, several *pregelatinized*

starches available are intended to be added in the dry form so that water alone can be used as the granulating solution. The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent. By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film which must be penetrated before the powders can be wetted by the binder solution. After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use. Since powders differ with respect to the ease with which they can be wetted, and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique it often is possible to gain effective binding with a lower concentration of binder.

The direct-compression method for preparing tablets (see page 1630) requires a material that not only is free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

Starch Paste—Corn starch is used widely as a binder. The concentration may vary from 10 to 20%. It usually is prepared as it is to be used by dispersing corn starch in sufficient cold purified water to make a 5 to 10% *w/w* suspension and warming in a water bath with continuous stirring until a translucent paste forms. It has been observed that during paste formation, not all of the starch is hydrolyzed. Starch paste then, is not only useful as a binder, but also as a method to incorporate some disintegrant inside the granules.

Gelatin Solution—Gelatin generally is used as a 10 to 20% solution; gelatin solutions should be prepared freshly as needed and used while warm or they will solidify. The gelatin is added to cold purified water and allowed to stand until it is hydrated. It then is warmed in a water bath to dissolve the gelatin, and the solution is made up to the final volume on a weight basis to give the concentration desired.

Cellulosic Solutions—Various cellulosics have been used as binders in solution form. Hydroxypropylmethylcellulose (HPMC) has been used widely in this regard. Typical of a number of cellulosics, HPMC is more soluble in cold water than hot. It also is more dispersable in hot water than cold. Hence, in order to obtain a good, smooth gel that is free from lumps or "fisheyes," it is necessary to add the HPMC in hot, almost boiling water and, under agitation, cool the mixture down as quickly as possible, as low as possible. Other water-soluble cellulosics such as hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) have been used successfully in solution as binders.

Not all cellulosics are soluble in water. Ethylcellulose can be used effectively when dissolved in alcohol, or as a dry binder which then is wetted with alcohol. It is used as a binder for materials that are moisture-sensitive.

Polyvinylpyrrolidone—PVP can be used as an aqueous or alcoholic solution and this versatility has increased its popularity. Concentrations range from 2% and vary considerably.

It will be noted that binder solutions usually are made up to weight rather than volume. This is to enable the formulator to determine the weight of the solids which have been added to the tablet granulation in the binding solution. This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent.

As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric in form. Because of this, the flow or spreadability of these solutions becomes important when selecting the appropriate granulating equipment. The rheology of polymeric solutions is a fascinating subject in and of itself, and should be considered for these materials.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations less than 1%. When used alone, talc may require concentrations as high as 5%. Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in "waterproofing" the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance.

The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies. Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant effectively will overcome this.

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant should be divided finely by passing it through a 60- to 100-mesh nylon cloth onto the granulation. In production this is called *bolting* the lubricant. After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles. Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Thus, attention to the mixing process itself is just as important as the selection of lubricant materials.

These process variables can be seen in the prolonged blending of a lubricant in a granulation. Overblending materially can affect the hardness, disintegration time and dissolution performance for the resultant tablets.

The quantity of lubricant varies, being as low as 0.1%, and in some cases as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and thus reduce the processing time.

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent. Perhaps the most widely investigated drug is acetylsalicylic acid. Different talcs varied significantly the stability of aspirin. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc and aluminum stearate.

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine and Carbowax 4000. However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility. While magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution. To overcome these waterproofing characteristics, sodium lauryl sulfate sometimes is included. One compound found to have the lubricating properties of magnesium stearate without its disadvantages is magnesium lauryl sulfate. Its safety for use in pharmaceuticals has not been established.

cium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol and microcrystalline cellulose. These commercially available direct-compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids. Dicalcium phosphate dihydrate (Di-Tab, *Stauffer*) in its unmilled form has good flow properties and compressibility. It is a white crystalline agglomerate insoluble in water and alcohol. The chemical is odorless, tasteless and nonhygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is Di-Pac (*Amstar*) prepared by the cocrystallization of 97% sucrose and 3% dextrins. Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow and its use is limited to tablet formulations prepared by the wet granulation method. Both anhydrous lactose and spray-dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets due to its pleasant taste and mouth-feel resulting from its negative heat of solution. In its granular form (*ICI Americas*) it has good flow and compressible qualities. It has a low moisture content and is not hygroscopic.

The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, *FMC*). This nonfibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades which range in average particle size from 20 to 100 μm. It is water insoluble but the material has the ability to draw fluid into a tablet by capillary action; it swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus requiring a lower level of lubricant as compared to other excipients.

Forced-flow feeders are mechanical devices available from pharmaceutical equipment manufacturers designed to deaerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained. See Fig 14.

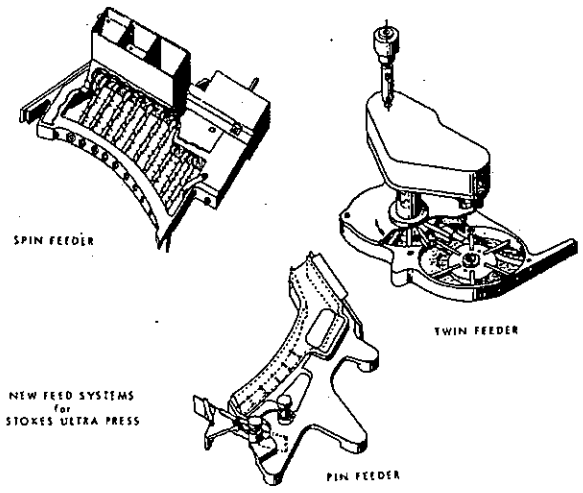

Fig 14. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes/Pennwalt).

Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as "forgiving" as were the older wet-granulated products. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression also is stimulating basic research on the flowability of powders with and without the presence of additives. Direct compression formulas are included in the formula section found on page 1636.

Related Granulation Processes

Spheronization—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment such as the Marumerizer (*Luwa*) and the CF-Granulator (*Vector*) is commercially available. A wet granulation containing the drug substance, diluent (if required) and binder, is passed first through an extruding machine to form rod-shaped cylindrical segments ranging in diameter from 0.5 to 12 mm. The segment diameter and the size of the final spherical particle depend on the extruder screen size. After extrusion the segments are placed into the Marumerizer where they are shaped into spheres by centrifugal and frictional forces on a rotating plate (see Fig 15). The pellets then are dried by conventional methods, mixed with suitable lubricants and compressed into tablets, or used as capsule-fill material. Microcrystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized.[35–38] The advantages of the process include the production of granules, regular in shape, size and surface characteristics; low friability resulting in fewer fines and dust; and the ability to regulate the size of the spheres within a narrow particle-size distribution.

Spheres also can be produced by fluid-bed granulation techniques and by other specialized equipment such as the CF-Granulator (*Vector*). These processes, however, must begin with crystals or nonpareil seeds followed by buildup. Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

Spray-Drying—A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying. The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed liquid may be a solution, slurry, emulsion, gel or paste, provided it is pumpable and capable of being atomized. As shown in Fig 16, the feed is sprayed into a current of warm filtered air. The air supplies the heat for

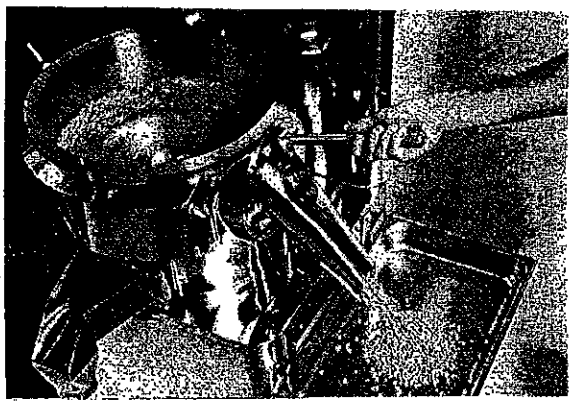

Fig 15. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

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Exhibit 51

Thermal Gelation Properties of Methyl and Hydroxypropyl Methylcellulose*

N. SARKAR, *Designed Polymers and Chemicals Research, The Dow Chemical Company, Midland, Michigan 48640*

Synopsis

Aqueous solutions of methyl and hydroxypropyl methylcellulose are known to gel upon heating. These gels are completely reversible in that they are formed upon heating yet will liquefy upon cooling. The precipitation temperature, gelation temperature, and gel strength of these methylcellulose solutions were determined as a function of molecular weight, degree of methyl and hydroxypropyl substitution, concentration, and presence of additives. The precipitation temperature of these polymer solutions decreases initially with increasing concentration until a critical concentration is reached above which the precipitation temperature is little affected by concentration changes. The incipient gelation temperature decreases linearly with concentration. The strength of these gels is time dependent, increases with increasing molecular weight, decreases with increasing hydroxypropyl substitution, and depends on the nature of additives. Hydrophobe–hydrophobe interaction or micellar interaction is postulated to be the cause of gelation. This thermal gelation property of the polymers is utilized in many end uses including food, pharmaceuticals, ceramics, tobacco, and other industrial applications.

INTRODUCTION

Thermally reversible gelation of aqueous solutions of macromolecules has been characterized as due to the formation of a three-dimensional crosslinked network structure.[1] Since this sol–gel transformation is reversible within a narrow temperature range, it does not involve the making or breaking of any covalent bonds, and the quasi-crosslinkages in the gel network structure are due to secondary valence forces as the solvent power of the medium decreases. Most macromolecules in solution exist as randomly coiled isolated chains. When the temperature is decreased or increased beyond the gelation temperature, and at appreciable concentrations, the polymer begins to reconstitute the original solid-state structure. Gelation is therefore an intermediate nonequilibrium metastable state in which a three-dimensional network structure is formed due to secondary valence forces. The mobility of the chain is greatly restricted and the reconstitution of the original solid state becomes an extremely slow process.

Some of the classical examples of natural polymers exhibiting the sol–gel transformation phenomenon are gelatin (collagen protein) and carrageenan (acidic polysaccharide). In these cases polymers exist as three-stranded (collagen) or two-stranded (carrageenan) helical rods which go into solution as random coils at elevated temperature. Upon cooling, a continuous network is formed due to partial formation of the helix.[2,3] Several synthetic polymers are also known to gel either in aqueous or organic medium. In many cases gels ex-

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hibit syneresis as the polymer network contracts on standing, liberating the pure solvent.

In contrast to these polymers, aqueous solutions of methylcellulose are known to gel when the temperature is increased.[4] Gelation of methyl or hydroxypropyl methylcellulose solution is primarily caused by the hydrophobic interaction between molecules containing methoxyl substitution. In a solution state at lower temperatures, molecules are hydrated and there is little polymer–polymer interaction other than simple entanglement. As the temperature is increased, the molecules gradually lose their water of hydration, which is reflected by a drop in the relative viscosity. Eventually, when a sufficient but not complete dehydration of the polymer occurs, a polymer–polymer association takes place and the system approaches an infinite network structure reflected by a sharp rise in relative viscosity. These gels are completely reversible in that they are formed upon heating yet will liquefy to the original consistency upon cooling.

There exists a certain degree of controversy regarding the mechanism of gelation of methylcellulose. The possibility of the gelation being caused by the presence of "long unaltered residues of original cellulose structure," as suggested by Ott and Spurlin,[5] is unlikely because for highly substituted methylcellulose, such as the one studied by Heyman,[4] there can be relatively few unsubstituted monomer units present. Solubility of methylcellulose, on the other hand,[5] is highly dependent on the uniformity of substitution. For example, uniformly substituted methylcelluloses prepared homogeneously from sodium cupricellulose or in quaternary base are water soluble at a much lower degree of substitution than are the ones made from alkali cellulose.

Observing that the gelation temperature increases with the decrease in methyl substitution, Vacher[6] concluded that the lack of trisubstitution was the cause of gelation. A lower gelation temperature can also be interpreted as resulting from increased hydrophobe–hydrophobe interaction with increasing methyl substitution. Rees[7] therefore accurately described these gels as "micellar gels" analogous to the nonionic surfactants, which also exhibit cloud points on heating.

The thermal gelation property of methyl and hydroxypropyl methylcellulose has promoted their use in a myriad of applications. Gelled, these cellulose ethers provide the binding and "green strength" necessary for workability for heat-setting reconstituted tobacco sheets and for extrusion of ceramic bodies. In many food applications the gelation properties of these cellulose ethers are used as binders and extrusion aids for reconstituted meat and vegetable products, foam stabilizers for foam mat drying, dough strengtheners for low-gluten bakery products, and grease barriers for fried foods. In many adhesive, coating, and printing techniques, the temporary gelation of these cellulose ethers provides viscosity control for high-temperature curing. In suspension polymerization, the gelation of these adsorbed cellulose ethers on the monomer droplets provides the stability of the suspension. In pharmaceutical application, gelation and gel strength of these ethers find their use in tablet coating and the manufacture of medicinal capsules.[8] A proper characterization of the gelation properties of these cellulose ethers is therefore essential in order to better utilize these properties in different end use applications.

EXPERIMENTAL

Material

Methylcellulose and hydroxypropyl methylcellulose samples used in this study were either commercial samples (Methocel* brand cellulose ethers) or samples made in the laboratory according to the procedure outlined in the literature.[9] Samples of methyl and hydroxypropyl methylcellulose were made having various degrees of substitution (D.S.) and molecular weights. Some of the commercial products used in this study are described at the top of Table I. In addition, the relationship between molecular weight and 2% aqueous solution viscosity at 20°C is also shown since it is convenient to describe molecular weight in terms of viscosity of a solution.

Procedures

The effects of shear rate and temperature on the viscosity of the solutions were obtained by using a Haake Rotovisco viscometer Model RV-3 (Haake, Inc., Saddlebrook, N.J.). Temperature and rate of temperature changes in the solutions during viscosity measurements were controlled by using a Tamson circulating bath fitted with a Neslab temperature programmer TP-2 (both from Neslab Instruments, Inc., Portsmouth, N.H.). The incipient gelation temperatures (IGT) of methylcellulose solutions were obtained by measuring the viscosity of the solution at a constant rate of shear as a function of temperature utilizing the temperature programmer at 0.25°C/min. The temperature at which the viscosity reaches a minimum is called the IGT. At or near the IGT, excessive shearing may break up the gel, giving a wrong gel point. As the temperature approaches the IGT, the rotation of the bob is stopped; and at increments of 2°C,

TABLE I
Substitution and Viscosity Ranges of Methocel Brand Cellulose Ethers[a]

Product designation suffix	Methoxyl degree of substitution DS	Hydroxypropyl molar substitution MS
A (η)	1.6–1.8	0
F (η)	1.6–1.8	0.1–0.2
E (η)	1.65–1.9	0.2–0.3
K (η)	1.1–1.4	0.1–0.3
η, cP	2% Viscosity range, cP	M_w Range
5	4–6	18,000– 22,000
25	20–30	48,000– 60,000
50	40–60	65,000– 80,000
100	80–120	85,000–100,000
400	350–550	120,000–150,000
1500	1200–1800	170,000–230,000
4000	3500–5500	300,000–500,000

[a] η Denotes viscosity of 2% solution at 20°C. The viscosity ranges and the corresponding molecular weight ranges are given in lower part of table.

* Trademark of The Dow Chemical Company.

the bob is turned on just for a few seconds to obtain the viscosity reading, thus minimizing gel structure breakdown.

Precipitation temperatures of methylcellulose solutions were determined by measuring the light transmission of the solution as a function of temperature using a Brinkman PC/1000 colorimeter (Brinkman Instruments, Westbury, N.Y.) which was modified in the following manner. The apparatus consists of 2.5-in.-diameter and 4.25-in.-long cylindrical aluminum block wound with 0.25-in.-O.D. copper tube through which water is circulated from a constant-temperature bath fitted with a temperature programmer as described before. The block has a 0.5-in.-diameter and 3-in.-long cavity at the center into which methylcellulose solution contained in a 13-mm-O.D. and 11-mm-I.D. Pyrex glass ampoule is placed. The ampoule is sealed to eliminate evaporation loss during heating. Two ⅛-in.-diameter flexible fiber glass light guides (Ealing Corp., South Natick, Mass.) are placed one at each end of the ampoule through the aluminum block making sure that the light guide tips are perfectly aligned and are perpendicular to the amopule. The other ends of the light guides are connected to the colorimeter, one to the light source and the other to the detector. The wavelength of light selected was 545 nm, at which minimum absorbance of light by methylcellulose solution was observed. The temperature of the solution was measured by placing a thermocouple in the aluminum block close to the ampoule. Initially, as the temperature was increased at a rate of 0.25°C/min, the light transmission remained at 100%, and then at some elevated temperature the light transmission began to decrease with increasing temperature. The temperatures at which light transmission reached 97.5% and 50% are called incipient precipitation temperature (IPT) and cloud point (CP), respectively.

Gel strengths of aqueous methylcellulose gels formed at 65°C were measured by using a cone Penetrometer (Precision Scientific Company, Chicago, Ill.) following the procedures of Haighton.[10] Cones were made of aluminum with tooled steel tips. Solutions contained in covered glass dishes were heated in a water bath at 65°C, and then the depths of penetration of the cones were measured by allowing the cone, preheated in a 65°C oven, to penetrate for 300 sec. During the measurement the gel dish and the cone were placed in a specially designed oven maintained at 65°C. The yield value of the gel was calculated from the following equation:

$$\tau_y = Kmg/h^2 \tag{1}$$

where τ_y is the yield value, g/cm²; m is the weight of the cone and the plunger rod, g; g is acceleration due to gravity; h is depth of penetration, cm; and k is the constant which depends only on the angle of the cone.

An exact expression for the constant K has been derived by Agranant and Volarovich,[11] and their equation is based upon a lengthy analysis of the plastic deformation during penetration. The Agranant equation was used to calculate the values of K, as shown in Table II.

TABLE II
Values of Constant K for Cones with Different Angle of the Cone

Cone angle	30°	45°	60°	90°	120°
K	0.959	0.416	0.214	0.0995	0.04

RESULTS AND DISCUSSIONS

Figure 1 is a curve showing the typical relationship between viscosity and temperature for a methylcellulose solution. As the temperature is increased, the viscosity of the solution decreases initially until the temperature reaches the incipient gelation temperature at which there is a sharp rise in viscosity, indicating gelation. The cooling curve, on the other hand, looks quite different. The viscosity increases on cooling, reaches a maximum, and then decreases until a slope inflection is reached as it merges with the original heating curve. Since gelation is a time-dependent kinetic phenomenon, the rates of heating and cooling and the rate of shear are very important in determining the shape of the curve. Ideally, in the absence of any large shearing forces and when the heating and cooling rates are extremely small, the minimum in the heating curve and the maximum in the cooling curve should appear at the same temperature, representing the true gelation temperature. In actual practice, it is very difficult to measure this true gelation temperature. As shown in Figure 1, the minimum in the heating curve and the maximum in the cooling curve could be 8–10°C apart, and the true gelation temperature is somewhere between the two temperatures.

Another phenomenon that is observed for the methylcellulose solutions on increasing temperature is the precipitation of the molecules as observed by the light transmission measurement. Figure 2 shows a typical precipitation phenomenon for aqueous solutions of a hydroxypropyl methylcellulose sample at different concentration. As the temperature is increased, the light transmission remains unchanged until, at the IPT, the light transmission deviates from 100% and sharply decreases on increasing temperature.

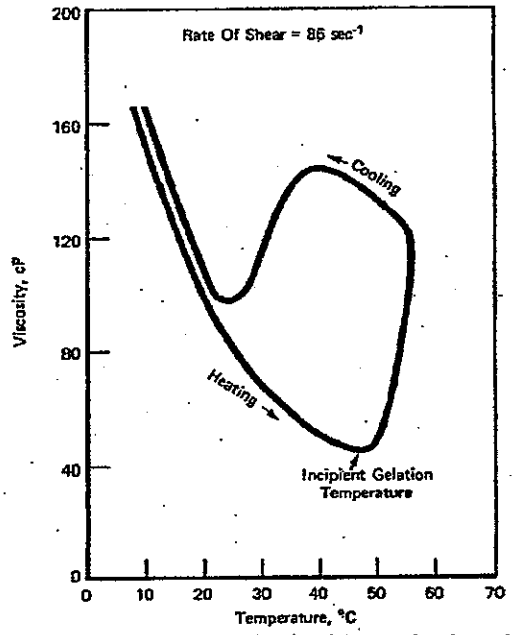

Fig. 1. Gelation of 2% aqueous solution of Methocel A100 on heating at 0.25°C/min.

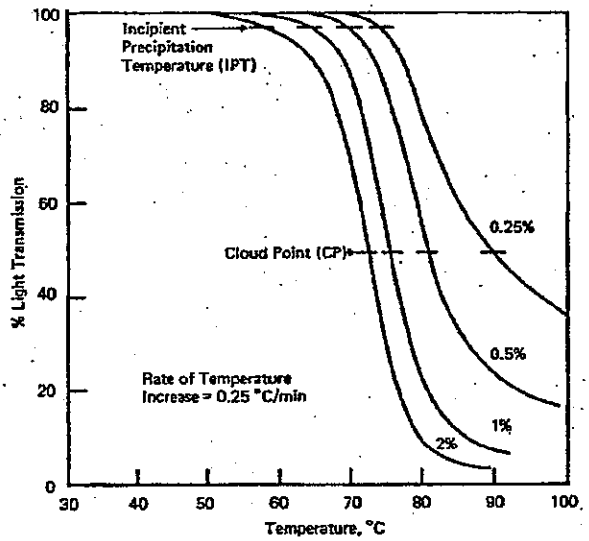

Fig. 2. An illustration of the change of 545 nm light transmission for aqueous solutions of a hydroxypropyl methylcellulose sample having a DS = 1.45 and MS = 0.11, as function of temperature at different concentrations.

This decrease in light transmission actually reflects the initial precipitation of the high molecular weight fractions. As the temperature is further increased, gradual fractionation of the molecules takes place. From that point of view neither the incipient precipitation temperature nor the cloud point actually reflects the precipitation temperature of the average molecular weight of the sample, but rather the precipitation temperature of an unknown molecular weight somewhat higher than the average molecular weight.

Figure 3 illustrates that both IPT and CP decrease initially as the concentration is increased; and then, after a certain critical concentration is reached, the precipitation temperatures are little affected by the concentration.

On the other hand, the incipient gelation temperature exhibits a linear relationship with concentration, as shown in Figure 4. It is also observed from Figure 4 that up to a concentration of about 6.5%, the hydroxypropyl methylcellulose solution becomes turbid before gelation occurs, while above 6.5% concentration the solutions gel before a turbidity becomes visible. Thus, it is conceivable that a methylcellulose solution of the right concentration could form a clear gel even at room temperature. This is in fact observed for low molecular weight methylcellulose solutions. This phenomenon is also true for high molecular weight methylcellulose solutions. But because of the physical difficulty in preparing highly concentrated solutions of high molecular weight methylcellulose, this phenomenon is difficult to observe.

As was mentioned earlier, gelation is a time-dependent phenomenon. When a solution of methylcellulose is heated above the incipient gelation temperature, the gel strength develops gradually with time. Figure 5 shows the rate of gel strength development for a 2% solution of methylcellulose at 65°C. It is observed that the gel strength increases with time and reaches the maximum gel strength

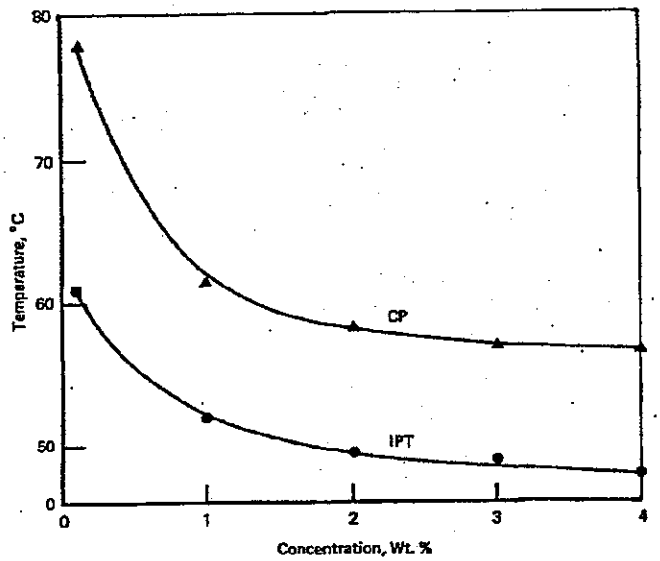

Fig. 3. Incipient precipitation temperature (IPT) and cloud point (CP) of Methocel F50 as function of concentration.

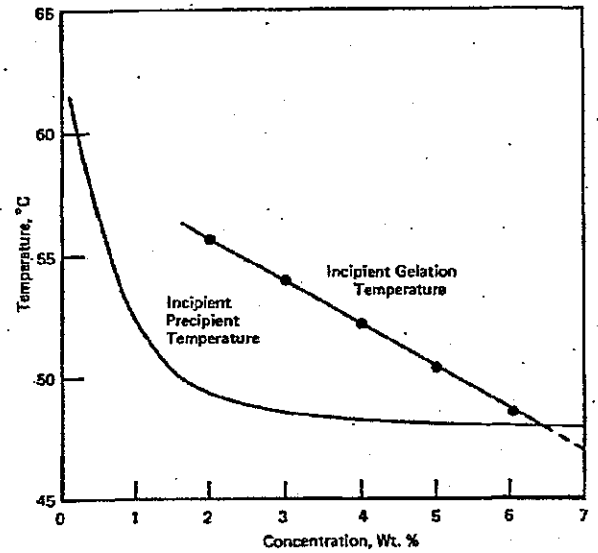

Fig. 4. Temperature of sol–gel transformation for aqueous solutions of Methocel F50 as function of concentration.

in about 3 hr, after which there was no change in strength. In general, when the gel is allowed to stand at that temperature for an extended period of time (more than a day), an observable syneresis of the gel takes place because of shrinkage

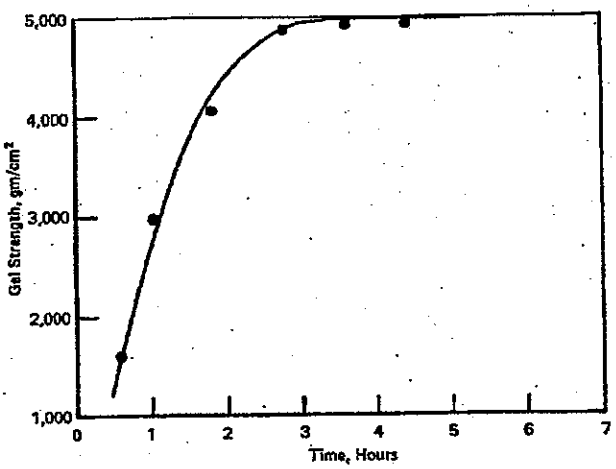

Fig. 5. Rate of gel strength development for 2% solution of Methocel A4C upon heating at 65°C.

of the three-dimensional structure. The syneresis is highly affected by temperature; and the higher the temperature and electrolyte concentration, the faster is the synerisis. So care was taken to measure gel strength before any syneresis was observed.

Gel characteristics of methylcellulose are known to vary considerably with type and degree of substitution, concentration, molecular weight, additives, etc. Depending on the type and total degree of substitution, both the gelation temperature and gel strength can vary considerably. In the following paragraphs some of these properties are discussed.

Effect of Molecular Weight

Table III shows the effect of molecular weight on the incipient gelation temperature, incipient precipitation temperature and the cloud point for 2% aqueous solutions of methylcellulose. It is interesting to note that within the molecular weight range studied there is no noticeable difference in the IGT, IPT, or CP. This is contrary to the classical polymer chemistry where one expects an increase

TABLE III
Gelation and Precipitation Temperatures of Methocel A Products as a Function of Molecular Weight

Molecular weight M_w	2% Solution viscosity at 20°C, cP	Gel point, °C	IPT, °C	CP, °C
~ 20,000	5.1	49.0	—	—
~ 38,000	15	—	43	63
~ 50,000	27.0	48.5	47	62
~ 90,000	98	48.5	—	—
~140,000	400	49.0	47	62
~400,000	4000	48.5	48	61

in precipitation temperature with decrease in molecular weight. Assuming that the concentrations of the solutions were too high to show true fractionation of the molecules, precipitation temperatures of Methocel A25 and Methocel A4M were measured at a concentration of 0.25%. The IPT and CP for Methocel A25 were 62°C and 85°C, respectively, while those for Methocel A4M were 63°C and >100°C, respectively. This is again the reverse of what one might expect for a normal polymer. This anomalous behavior of methylcellulose solution can however be explained if one takes into account the molecular weight distribution and the state of aggregation of the polymer in solution.

All the methylcellulose samples have a wide molecular weight distribution where the ratio of weight- to number-average molecular weight may vary from 3 to as high as 10 depending on the type of pulp used and the processing conditions. The incipient gelation temperature and the incipient precipitation temperature actually reflect the influence of the high molecular weight fraction of the sample which precipitates out first. All the samples of varying average molecular weight contain similar high molecular weight fractions, although of varying amounts. This is the reason why all these samples are exhibiting similar gelation and precipitation temperatures.

On the other hand, the anomaly observed at low concentration by low molecular weight methylcellulose (Methocel A25) exhibiting lower cloud point than the high molecular weight sample (Methocel A4M) can only be explained by the presence of aggregates in solution. Neely[12] and Kuhn et al.[13] observed that aqueous methylcellulose solution even at room temperature contains aggregates. Kuhn et al.[13] suggested that the low molecular weight methylcellulose, because of its rod-like structure, can aggregate more via parallel arrangement along the chain than the high molecular weight polymer, having a random coil configuration. This can result in the observed lowering of cloud point when the molecular weight is decreased.

In an attempt to eliminate the aggregates in solution by cooling, two methylcellulose solutions of 2% concentration and having viscosity of 26000 cP and 10 cP, respectively, at 20°C were stored in a refrigerator at 4°C for a week just prior to precipitation temperature measurement. While the incipient precipitation temperature remained the same at 43.5°C for these two samples, the cloud points of 26000-cP and 10-cP methylcellulose samples were 56.5 and 59°C, respectively. This confirms the aggregation theory and indicates that the aggregates can be dispersed, if not completely, by cooling the solutions.

Gel strength of methylcellulose solution, on the other hand, is dependent on molecular weight, as shown in Figure 6. The gel strength increases with increasing molecular weight and gradually levels off at or above an average molecular weight of 140,000 (Methocel A4C). Compared to these results, a linear relationship is found between the logarithm of viscosity and the logarithm of molecular weight. While this independence of gel strength above a certain molecular weight is difficult to explain from a mechanistic point of view, these results are similar to those observed with gelatin.[14] These results are also analogous to the relationship between the strength of native cellulose fibers and their DP (degree of polymerization),[15] in which the strength of acid-treated cotton increases with DP and then finally levels off at a DP between 700 and 1000. Surprisingly, the molecular weight of 140,000 for methylcellulose also corresponds to a DP of 760.

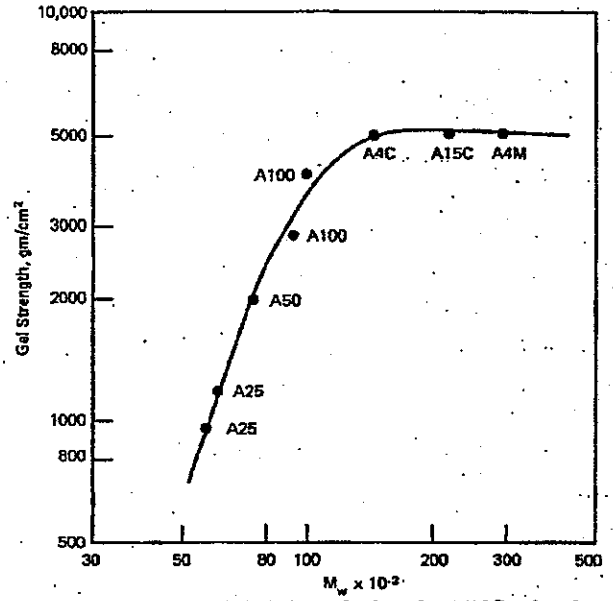

Fig. 6. Gel strength of 2% aqueous methylcellulose gels after 4 hr at 65°C as function of molecular weight. Numbers designate Methocel A samples of different viscosity grades.

Effect of Substitution

Table IV shows the precipitation temperatures of different hydroxypropyl methylcellulose samples having DS and MS as shown in Table I, and of different molecular weight. Here again no significant difference in IPT is observed, indicating the influence of molecular weight distribution. On the other hand, cloud points show a normal decrease with increase in molecular weight, indicating that the aggregation phenomenon in these samples is not as predominant as was observed with methylcellulose samples. Effect of total degree of substitution and the hydroxypropyl substitution is also observed as the cloud point, for the similar viscosity-grade products, decreases in the order K > F > E products, and the values are larger than observed with methylcellulose samples.

TABLE IV
Precipitation Temperatures of 2% Aqueous Solutions of Different Methocel Brand Cellulose Ethers Having Different Molecular Weight and Substitution

Methocel brand	IPT, °C	CP, °C
E15	61	67
E50	61	64
E4M	58	61
F50	61	69
F4M	60	65
K35	61	79
K100	60	76
K4M	61	70

It is quite well known that the type of substitution is important in determining the gelation properties of cellulose ethers. For example, carboxymethyl cellulose, sulfoethyl cellulose, and hydroxyethyl cellulose are all nongelling types. Hydroxypropyl cellulose does not show gelation but does precipitate out of solution on heating. Hydroxyethyl methylcellulose, containing a high degree of methoxyl and a low degree of hydroxyethyl substitution, is known to exhibit gelation, but the polymer containing a high degree of hydroxyethyl and a low degree of methoxyl substitution does not gel. Apparently, while it is the methoxyl substitution in hydroxypropyl methylcellulose which is responsible for its gelation, the hydroxypropyl substitution is also responsible for altering the gelation characteristics significantly.

Figure 7 shows the incipient gelation temperature-versus-concentration relationship for three different Methocel brand products. While the relationship is linear for all, their slopes are quite different. All these products have a similar methoxyl degree of substitution (1.7–1.9), while Methocel A, F, and E have hydroxypropyl molar substitution of 0, 0.13, and 0.22, respectively. These data indicate that the differences in IGT at low concentrations are not very significant. But as the concentration increases, IGT diverge. Thus, methylcellulose (Methocel A) gels at room temperature when the concentration reaches about 12%, while the hydroxypropyl methylcellulose gels at room temperature only when the concentrations are significantly higher.

If one maintains the hydroxypropyl substitution constant, say, at about MS = 0.22 and lowers the methyl substitution, the gel point increases gradually due to lower total degree of substitution and hence lower hydrophobe–hydrophobe interaction. For example, Methocel K (methoxyl D.S. = 1.1–1.4, and hydroxypropyl M.S. = 0.1–0.3) gels at 70–90°C. It has also been observed that lowering the methoxyl substitution produces gels that are mushy in character with yield value so low that data could not be generated using the cone penetrometer.

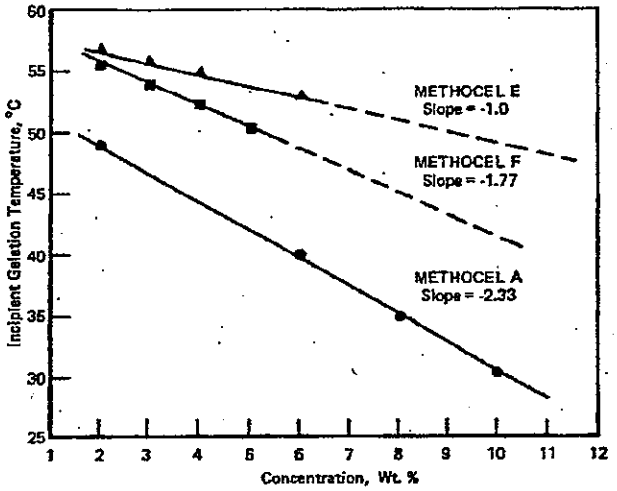

Fig. 7. Incipient gelation temperature of different Methocel products as function of concentration.

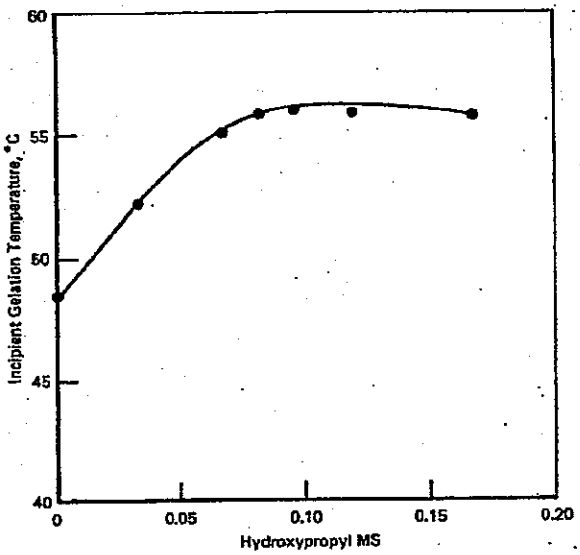

Fig. 8. Incipient gelation temperatures of hydroxypropyl methylcellulose as function of hydroxypropyl molar substitution. Methoxyl DS = 1.63–1.88; 2% solution viscosity = 400–8000 cP.

Figure 8 shows the effect of hydroxypropyl substitution (MS) on IGT for 2% solutions of hydroxypropyl methylcellulose. In this experiment methoxyl DS was kept at 1.63–1.88, and the 2% solution viscosity of the samples at 20°C were between 400 and 8000 cps. Since IGT is not dependent on molecular weight at these viscosity ranges, the data actually show the effect of hydroxypropyl MS. It is seen from Figure 8 that as the hydroxypropyl MS is increased, the IGT increases slightly, reaches a maximum at about 0.1 MS, and then decreases very slightly with increasing MS. Overall, there is not a drastic change in IGT between 0 and 0.2 MS.

In contrast, the effect of hydroxypropyl MS on gel strength is significant, as shown in Figure 9. Straight methylcellulose with a DS of 1.63–1.88 has a very high gel strength. As the hydroxypropyl substitution increases, the gel strength decreases drastically until at MS = 0.15 and above the gels become mushy.

These results are a little difficult to explain from the point of view of mechanism. Both the methoxyl and hydroxypropyl substitutions render the cellulose hydrophobic. The higher gelation temperature and lower gel strength of methylcellulose upon increasing hydroxypropyl substitution can therefore be due only to steric reasons. On the other hand, keeping the hydroxypropyl substitution constant while decreasing the methoxyl substitution renders the polymer hydrophilic because of decreased total degree of substitution. This also results in increased gelation temperature and decreased gel strength. Thus, by varying the type and DS of the substituent groups, various temperature behaviors of hydroxypropyl methylcellulose can be achieved.

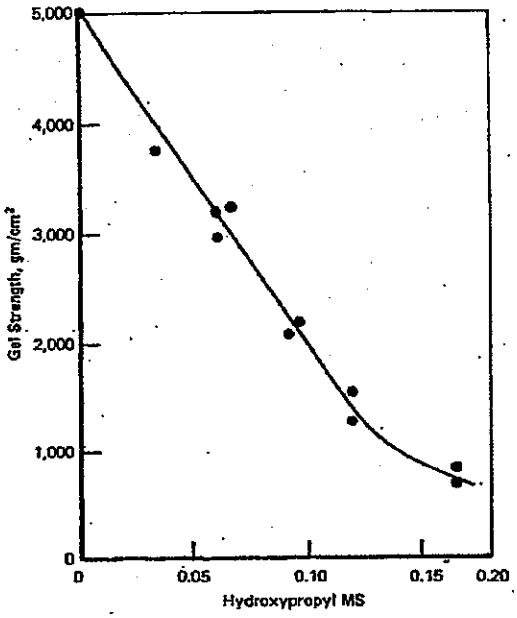

Fig. 9. Gel strength of 2% aqueous HPMC gels after 4 hr at 65°C as function of hydroxypropyl molar substitution. Methoxyl DS = 1.63–1.88; 2% solution viscosity = 400–8000 cP.

Effect of Additives

Gelation properties of methylcellulose can be substantially altered by the use of additives.[16,17] Most electrolytes, as well as sucrose, glycerol, etc., depress the gel point owing to their greater affinity for water, thus dehydrating the polymer. A few compounds, such as ethanol and propylene glycol, act to elevate the gel point. Although these compounds have greater affinity for water than the cellulosic polymers, they act as solubilizers due to their solvent power (or cohesive energy density) and increase the gelation temperature.

The precipitation temperature of a methylcellulose solution is also known to increase in the presence of urea.[18] Water is normally hydrogen bonded to the polymer. Urea molecules act on the hydrogen bond and attach themselves to the polymer by displacing water molecules. Dissociation of the urea molecules takes place at a considerably higher temperature than the dehydration temperature.

In this paper the effect of sodium chloride on the gel point and gel strength is described in more detail. Figure 10 illustrates the effect of sodium chloride on the gel point, incipient precipitation temperature, and gel strength (after heating at 65°C for 3 hr) for a 2% methylcellulose solution, indicating that sodium chloride considerably lowers the gelation and precipitation temperature of the solutions. On the other hand, there is a significant increase in gel strength on increasing salt concentration.

This reduced solubility behavior of organic nonelectrolyte in water by the addition of neutral salts is quite well known. This "salting out" was once thought of as due to the competition between the polymer and the electrolyte for the water

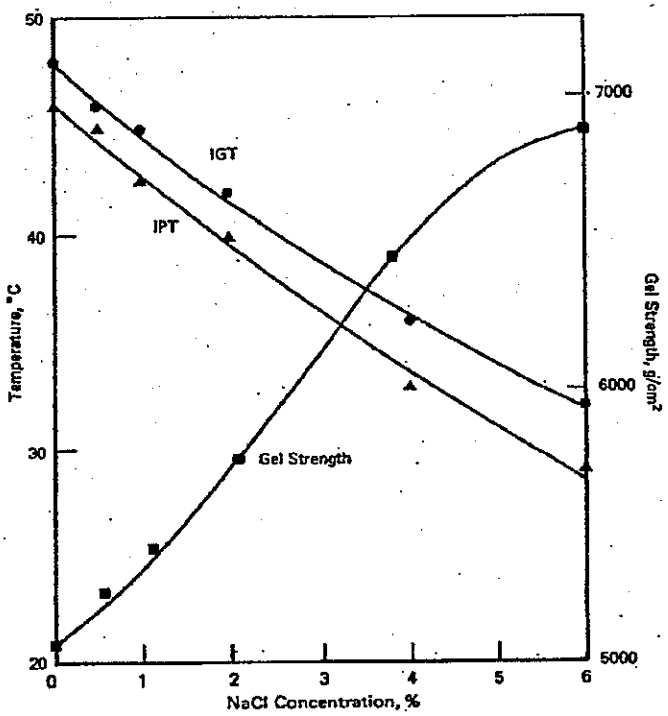

Fig. 10. Incipient gelation temperature (IGT), incipient precipitation temperature, and gel strength of 2% methylcellulose (Methocel A15C) solution as function of NaCl concentration.

molecules. However, the phenomenon is more complex, since the relative "salting out efficiency" of different salts varies widely with the nonelectrolyte polymer.[19] Solvent power of electrolyte solution depends strongly on both cations and anions, increasing with the polarizability of the anion. Stanton et al.[20] studied a series of electrolytes and tabulated them in terms of solvent power of these aqueous salt solutions for nonelectrolyte polymers. Utilizing their table, the gelation properties of methylcellulose solution can also be approximately predicted as a function of electrolyte types. Any additive that increases the solvent power of water for the polymer would elevate the gelation temperature, and vice versa.

In conclusion, we now have a better understanding of the gelation properties of methyl and hydroxypropyl methylcellulose. However, we are still a long way from a complete understanding of these very interesting properties and their correlation with varied end use applications. Such studies will be continued and reported at appropriate intervals.

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Exhibit 52

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Exhibit 53

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Exhibit 54

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Exhibit 55

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Exhibit 56

Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose

2 Synonyms

Avicel PH; *Celex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; E460; *Emcocel*; *Ethispheres*; *Fibrocel*; *Pharmacel*; *Tabulose*; *Vivapur*.

3 Chemical Name and CAS Registry Number

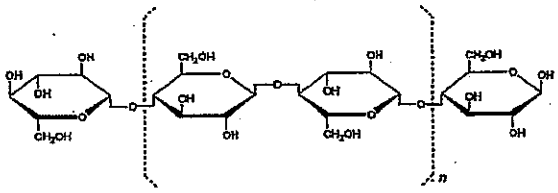
Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$
where $n \approx 220$.

Molecular Weight: ≈36 000

5 Structural Formula



6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products; *see* Table I.

8 Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2002 Suppl 4.2	USPNF 20
Identification	+	+	+
Characters	+	+	—
pH	5.0–7.0	5.0–7.5	5.0–7.0
Bulk density	+	—	+
Loss on drying	≤7.0%	≤6.0%	≤7.0%
Residue on ignition	≤0.05%	—	≤0.05%
Conductivity	+	—	+
Sulfated ash	—	≤0.1%	—
Ether-soluble substances	≤0.05%	≤0.05%	≤0.05%
Water-soluble substances	+	≤0.25%	≤0.24%
Heavy metals	≤10 ppm	≤10 ppm	≤0.001%
Starch	—	+	—
Organic volatile impurities	—	—	+
Microbial limits	+	+	+

10 Typical Properties

Angle of repose:
49° for *Ceolus KG*
34.4° for *Emcocel 90M*[9]

Density (bulk):
0.337 g/cm^3
0.32 g/cm^3 for *Avicel PH-101*[10]
0.29 g/cm^3 for *Emcocel 90M*[9]

Density (tapped):
0.478 g/cm^3
0.45 g/cm^3 for *Avicel PH-101*[10]
0.35 g/cm^3 for *Emcocel 90M*[9]

Density (true): 1.512–1.668 g/cm^3

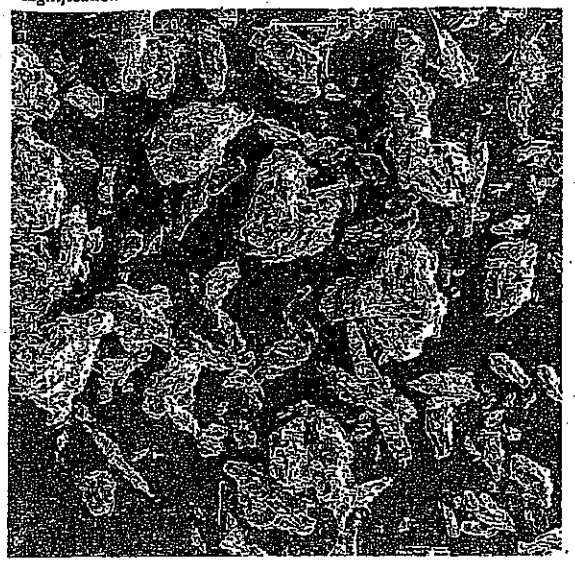
Flowability: 1.41 g/s for *Emcocel 90M*.[9]

Melting point: chars at 260–270°C.

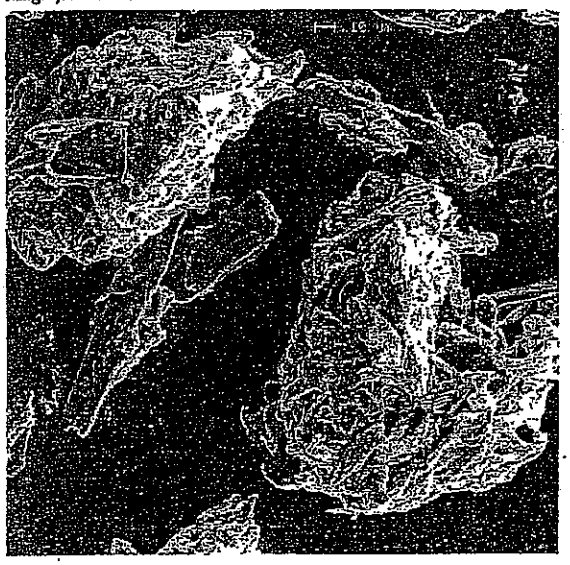
Moisture content: typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.[11] *See* Table III.

Particle size distribution: typical mean particle size is 20–200 µm. Different grades may have a different nominal mean particle size; *see* Table III.

SEM: 1
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals Co.
Lot No.: 98662
Magnification: 100 ×



SEM: 2
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals Co.
Lot No.: 98662
Magnification: 300 ×



Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Specific surface area:
1.06–1.12 m^2/g for *Avicel PH-101*
1.21–1.30 m^2/g for *Avicel PH-102*
0.78–1.18 m^2/g for *Avicel PH-200*

11 Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

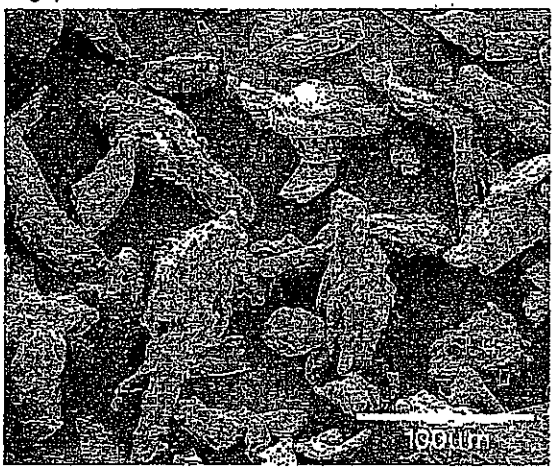
Microcrystalline cellulose is incompatible with strong oxidizing agents.

Table III: Properties of selected commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101[a]	50	60	≤1.0	≤5.0
		200	≤30.0	
Avicel PH-102[a]	100	60	≤8.0	≤5.0
		200	≥45.0	
Avicel PH-103[a]	50	60	≤1.0	≤3.0
		200	≤30.0	
Avicel PH-105[a]	20	400	≤1.0	≤5.0
Avicel PH-112[a]	100	60	≤8.0	≤1.5
Avicel PH-113[a]	50	60	≤1.0	≤1.5
		200	≤30.0	
Avicel PH-200[a]	180	60	≥10.0	≤5.0
		100	≥50.0	
Avicel PH-301[a]	50	60	≤1.0	≤5.0
		200	≤30.0	
Avicel PH-302[a]	100	60	≤8.0	≤5.0
		200	≥45.0	
Celex 101[b]	75	60	≤1.0	≤5.0
		200	≥30.0	
Ceolus KG-802[c]	50	60	≤0.5	≤6.0
		200	≤30.0	
Emcocel 50M[d]	51	60	≤0.25	≤5.0
		200	≤30.0	
Emcocel 90M[d]	91	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 101[e]	50	60	≤1.0	≤5.0
		200	≤30.0	
Vivapur 102[e]	90	60	≤8.0	≤5.0
		200	≥45.0	
Vivapur 12[e]	160	38	≤1.0	≤5.0
		94	≤50.0	

Suppliers: [a]FMC Biopolymer; [b]International Specialty Products; [c]Asahi Kasei Corporation; [d]Penwest Pharmaceuticals Co.; [e]J. Rettenmaier & Söhne GmbH.

SEM: 3
Excipient: Microcrystalline cellulose
Manufacturer: FMC Biopolymer
Magnification: 100×



13 Method of Manufacture

Microcrystalline cellulose is manufactured by the controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14 Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.[13]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxymethylcellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose; silicified microcrystalline cellulose.

Microcrystalline cellulose and carrageenan

Synonyms: *Lustre Clear.*
Comments: *Lustre Clear* (FMC Biopolymer) is an aqueous film coating combining microcrystalline cellulose and carrageenan.

Microcrystalline cellulose and carboxymethylcellulose sodium

Synonyms: *Avicel CL-611*; *Avicel RC-581*; *Avicel RC-591*; colloidal cellulose; dispersible cellulose.
Appearance: white, odorless and tasteless, hygroscopic powder.
Acidity/alkalinity: pH = 6–8 for a 1.2% w/v aqueous dispersion.
Moisture content: not more than 6.0% w/w.
Particle size distribution:
Avicel CL-611: ≤0.1% retained on a #60 mesh and ≤50% retained on a #325 mesh
Avicel RC-581: ≤0.1% retained on a #60 mesh and ≤35% retained on a #200 mesh
Avicel RC-591: ≤0.1% retained on a #60 mesh and ≤45% retained on a #325 mesh
Solubility: practically insoluble in dilute acids and organic solvents. Partially soluble in dilute alkali and water (carboxymethylcellulose sodium fraction).
Viscosity (dynamic):
5–20 mPa s (5–20 cP) for a 1.2% w/v aqueous dispersion of *Avicel CL-611*
72–168 mPa s (72–168 cP) for *Avicel RC-581* at the same concentration
39–91 mPa s (39–91 cP) for *Avicel RC-591* at the same concentration
Comments: mixtures of microcrystalline cellulose and carboxymethylcellulose sodium that are dispersible in water and produce thixotropic gels are suitable as suspending vehicles in pharmaceutical formulations. The amount of carboxymethylcellulose present can vary between 8.3% and 18.8% w/w depending upon the grade of material.

Microcrystalline cellulose and guar gum

Synonyms: *Avicel CE-15.*
Comments: *Avicel CE-15* (FMC Biopolymer) is a coprocessed mixture of microcrystalline cellulose and guar gum used in chewable tablet formulations.

18 Comments

Several different grades of microcrystalline cellulose are commercially available that differ in their method of manufacture,[14,15] particle size, moisture, flow, and other physical properties.[16–25] The larger-particle-size grades generally provide better flow properties in pharmaceutical machinery. Low-moisture grades are used with moisture-sensitive materials. Higher-density grades have improved flowability.

Several coprocessed mixtures of microcrystalline cellulose with other excipients such as carrageenan, carboxymethylcellulose sodium, and guar gum are commercially available; *see* Section 17.

Celphere (Asahi Kasei Corporation) is a pure spheronized microcrystalline cellulose available in several different particle size ranges.

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Handbook of Pharmaceutical Excipients

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Handbook of Pharmaceutical Excipients

Exhibit 57

Sugar Spheres

1 Nonproprietary Names

BP: Sugar spheres
PhEur: Sacchari spheri
USPNF: Sugar spheres

2 Synonyms

Non-pareil; non-pareil seeds; *NPTAB*; *Nu-Core*; *Nu-Pareil PG*; sugar seeds; *Suglets*.

3 Chemical Name and CAS Registry Number

—

4 Empirical Formula Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations.[1–4] They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.

Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating.

Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8 Description

The USPNF 20 describes sugar spheres as approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch.

The PhEur 2002 states that sugar spheres contain not more than 92% of sucrose calculated on the dried basis. The remainder consists of corn (maize) starch and may also contain starch hydrolysates and color additives. The diameter of sugar spheres varies from 200 to 2000 µm and the upper and lower limits of the size of the sugar spheres are stated on the label.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sugar spheres.

Test	PhEur 2002	USPNF 20
Identification	+	+
Heavy metals	≤5 ppm	≤5 ppm
Loss on drying	≤5.0%	≤4.0%
Microbial limits	+	+
Organic volatile impurities	—	+
Particle size distribution	+	+
Residue on ignition	≤0.2%	≤0.25%
Specific rotation	—	+41° to +61°
Sucrose (dried basis)	≤92%	62.5–91.5%

10 Typical properties

Density:
1.57–1.59 g/cm^3 for *Suglets* less than 500 µm in size
1.55–1.58 g/cm^3 for *Suglets* more than 500 µm in size

Flowability: <10 seconds, free flowing.

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available from various suppliers (US standard sieves):

45–60 mesh (250–355 µm)
40–50 mesh (300–425 µm)
35–45 mesh (355–500 µm)
35–40 mesh (420–500 µm)
30–35 mesh (500–600 µm)
25–30 mesh (610–710 µm)
20–25 mesh (710–850 µm)
18–20 mesh (850–1000 µm)
16–20 mesh (850–1180 µm)
14–18 mesh (1000–1400 µm)

Solubility: solubility in water varies according to the sucrose-to-starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.

Specific surface area:
0.1–0.2 m^2/g for *Suglets* less than 500 µm in size
>0.2 m^2/g for *Suglets* more than 500 µm in size

11 Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Starch and Sucrose for information concerning the incompatibilities of the component materials of sugar spheres.

13 Method of Manufacture

Sugar spheres are prepared from crystalline sucrose, which is coated using sugar syrup and a starch dusting powder.

14 Safety

Sugar spheres are used in oral pharmaceutical formulations. The sucrose and starch components of sugar spheres are widely used in edible food products and oral pharmaceutical formulations.

The adverse reactions and precautions necessary with the starch and sucrose components should be considered in any product containing sugar spheres. For example, sucrose is generally regarded as more cariogenic than other carbohydrates, and in higher doses is also contraindicated in diabetic patients.

See Starch and Sucrose for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK and Europe. The sucrose and starch components of sugar spheres are individually approved for use as food additives in Europe and the USA.

17 Related Substances

Compressible sugar; confectioner's sugar; starch; sucrose.

18 Comments

—

19 Specific References

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Exhibit 58

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2- pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula Molecular Weight

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 25 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, ranging from 10 to 120. The *K*-value is calculated using Fikentscher's equation:[1]

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value × 10^{-3}, and c is the concentration in % w/v.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} = \sqrt{\frac{300c\log z(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value × 10^{-3}, and c is the concentration in % w/v.

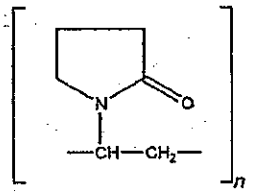
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[4–6] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. *See* Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; *see* Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for povidone.

Test	JP 2001	PhEur 2002 (Suppl 4.3)	USP 25
Identification	+	+	+
Characters	—	+	—
pH	—	—	3.0–7.0
$K \leqslant 30$	3.0–5.0	3.0–5.0	—
$K > 30$	4.0–7.0	4.0–7.0	—
Appearance of solution	+	+	—
Viscosity	—	+	—
Water	⩽5.0%	⩽5.0%	⩽5.0%
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Lead	—	—	⩽10 ppm
Aldehydes	⩽500 ppm[a]	⩽500 ppm[a]	⩽0.05%
Hydrazine	⩽1 ppm	⩽1 ppm	⩽1 ppm
Vinylpyrrolidinone	⩽10 ppm	⩽10 ppm	⩽0.2%
Peroxides	⩽400 ppm[b]	⩽400 ppm[b]	—
K-value	25–90	—	10–120
⩽15	90.0–108.0%	85.0–115.0%	85.0–115.0%
>15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	⩽10 ppm	⩽10 ppm	—
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

[a] Expressed as acetaldehyde.
[b] Expressed as hydrogen peroxide.

10 Typical Properties

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk): 0.29–0.39 g/cm^3 for *Plasdone*.
Density (tapped): 0.39–0.54 g/cm^3 for *Plasdone*.
Density (true): 1.180 g/cm^3
Flowability:
20 g/s for povidone K-15
16 g/s for povidone K-29/32
Melting point: softens at 150°C.
Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figures 1 and 2.

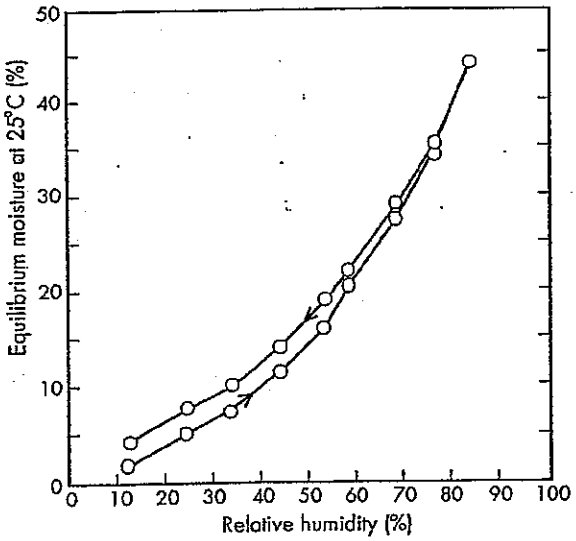


Figure 1: Sorption–desorption isotherm of povidone K-15 (*Plasdone K-15*).

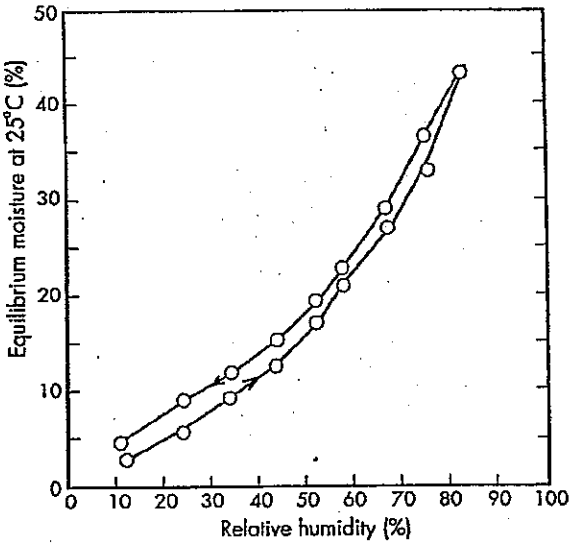


Figure 2: Sorption–desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*).

Particle size distribution:
Kollidon 25/30: 90% >50 µm, 50% >100 µm, 5% >200 µm
Kollidon 90: 90% >200 µm, 95% >250 µm[7]
Solubility: freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.
Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. *See* Tables IV and V.[7]

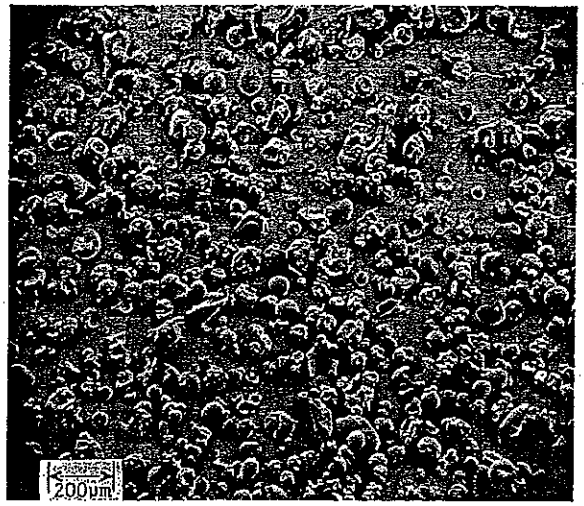
Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.[7]

Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

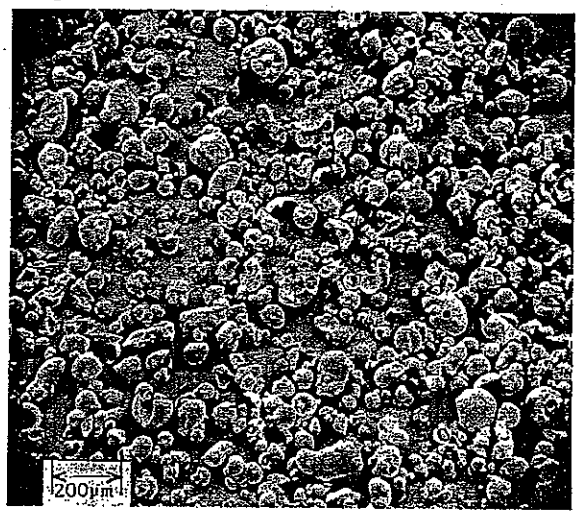
Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol and propan-2-ol at 25°C.[7]

Grade	Dynamic viscosity (mPa s)	
	Ethanol	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

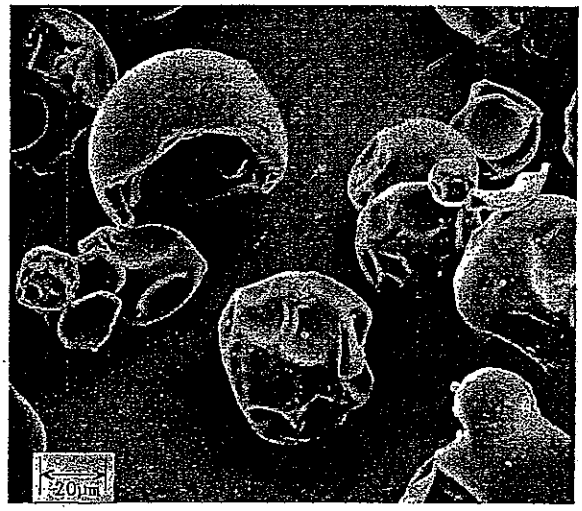
SEM: 1
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 60×
Voltage: 5 kV



SEM: 3
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 60×
Voltage: 5 kV

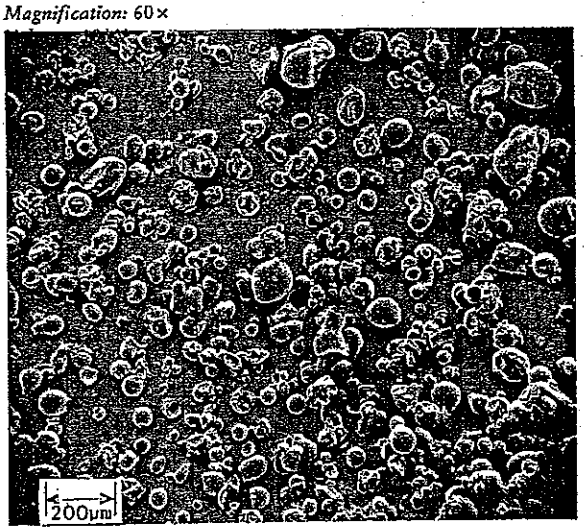


SEM: 2
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 600×
Voltage: 5 kV



SEM: 4
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 600×
Voltage: 10 kV

SEM: 5
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 60×



SEM: 6
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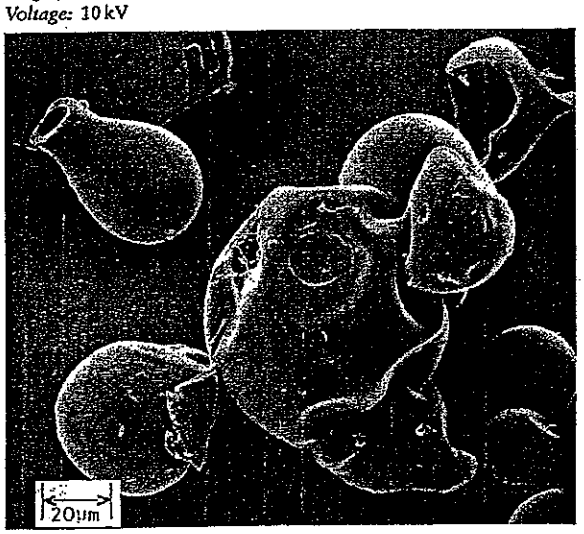
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 600×
Voltage: 10 kV



SEM: 7
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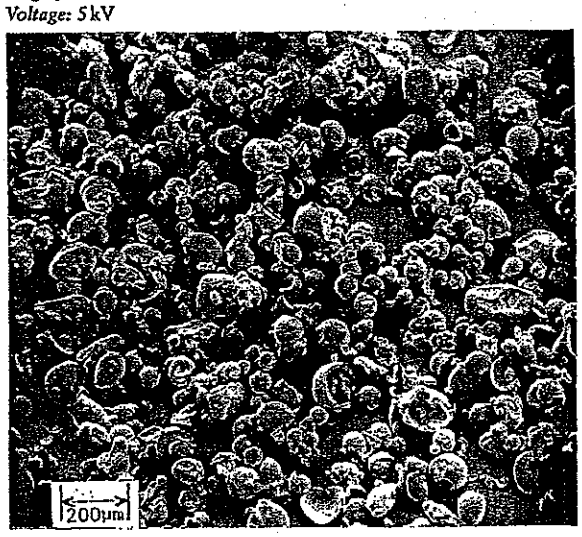
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 60×
Voltage: 5 kV



SEM: 8
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 600×
Voltage: 10 kV

11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous

solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g., thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[8]

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.[8] Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.[9] Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.[10]

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.[11]

LD_{50} (mouse, IP): 12 g/kg[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Crospovidone.

18 Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone–iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations.

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Exhibit 59

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Exhibit 60

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Exhibit 61

US005885616A

United States Patent [19]

Hsiao et al.

[11] Patent Number: 5,885,616

[45] Date of Patent: Mar. 23, 1999

[54] **SUSTAINED RELEASE DRUG DELIVERY SYSTEM SUITABLE FOR ORAL ADMINISTRATION**

[75] Inventors: **John Hsiao**, Livermore; **I-Lan Sue**, San Jose, both of Calif.

[73] Assignee: **Impax Pharmaceuticals, Inc.**, Hayward, Calif.

[21] Appl. No.: 912,722

[22] Filed: Aug. 18, 1997

[51] Int. Cl.[6] A61K 9/24

[52] U.S. Cl. 424/472; 424/461; 424/490; 424/494; 424/495; 424/497

[58] Field of Search 424/472, 490, 424/495, 494, 497, 461

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OTHER PUBLICATIONS

{711} Dissolution; USP 23; Physical Tests {711} 1791–1794, 2185,3208–3209, 2577–2578, 3794–3495, 2833–2834.

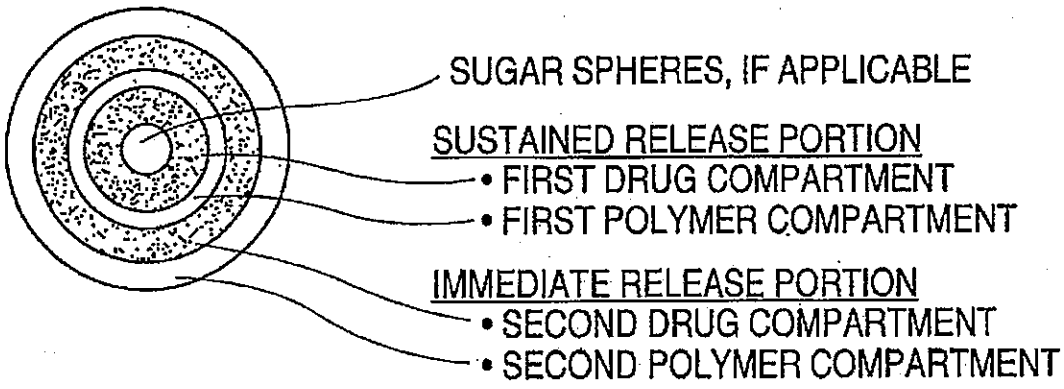
{724} Drug Release; USP 23; Physical Tests 1793–1799, 2534–2536, 2709–2715, 3012–3017, 3209–3215, 3468–3474.

Primary Examiner—Thurman K. Page
Assistant Examiner—Brian K. Seidleck
Attorney, Agent, or Firm—Arter & Hadden, LLP

[57] ABSTRACT

A single bead drug delivery system suitable for oral administration with multiply layered drug and polymer compartments can provide a two-step release of active agent to facilitate an immediate yet sustained drug delivery over a 24 hour period following oral administration with minimized variance between peak and trough levels of therapeutic drug amounts.

20 Claims, 4 Drawing Sheets



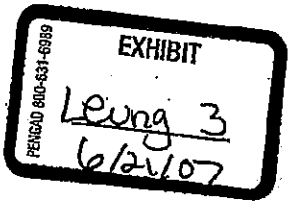


FIG. 1

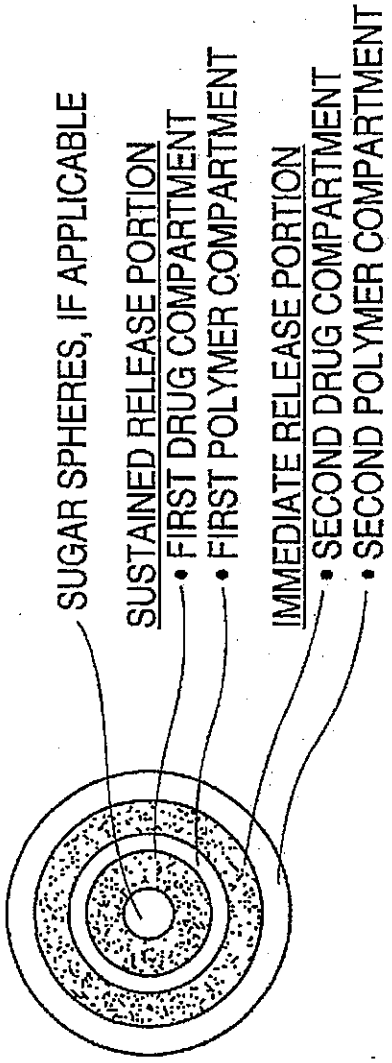

SUGAR SPHERES, IF APPLICABLE
SUSTAINED RELEASE PORTION
• FIRST DRUG COMPARTMENT
• FIRST POLYMER COMPARTMENT
IMMEDIATE RELEASE PORTION
• SECOND DRUG COMPARTMENT
• SECOND POLYMER COMPARTMENT

FIG. 2

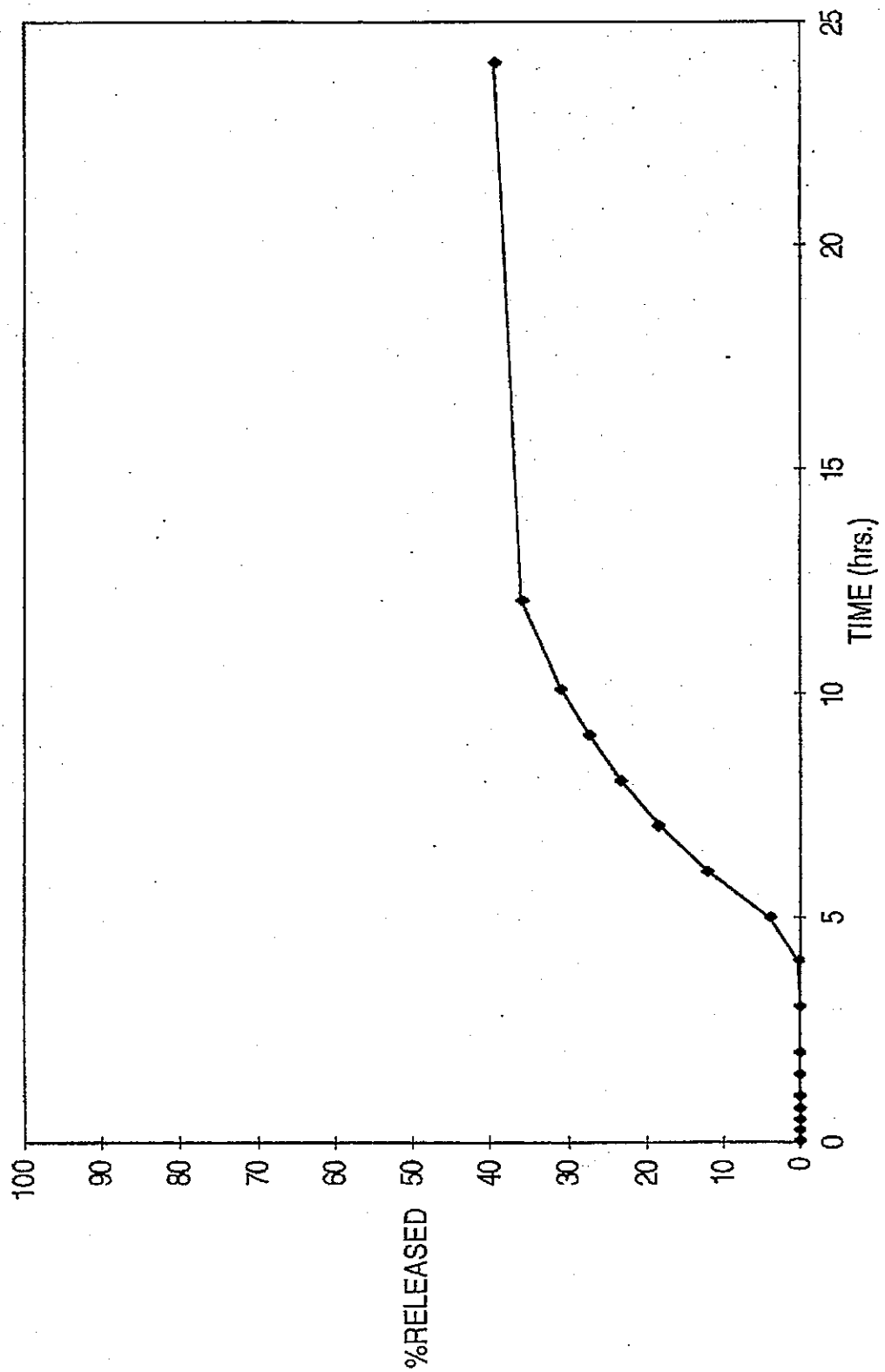


FIG. 3

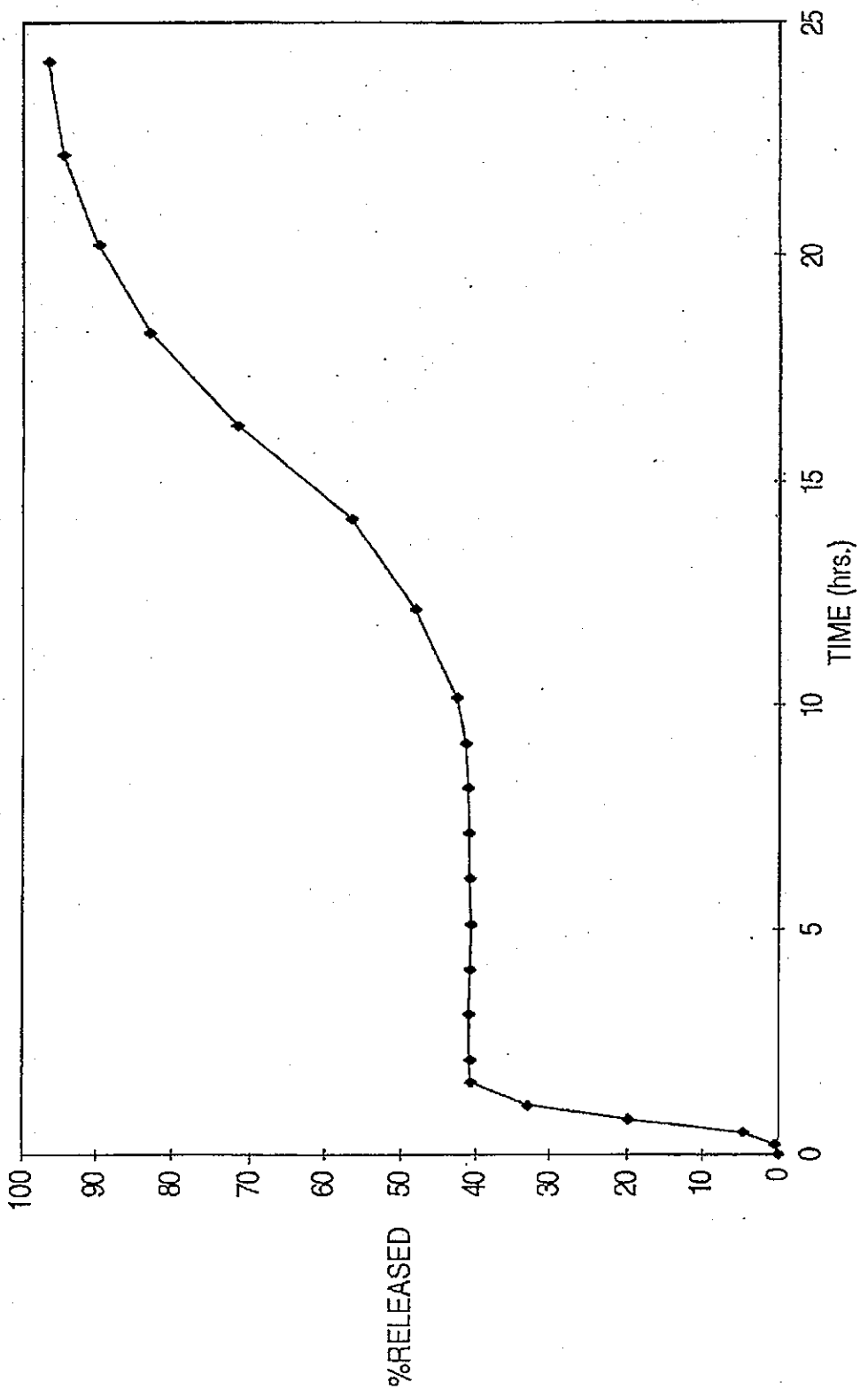
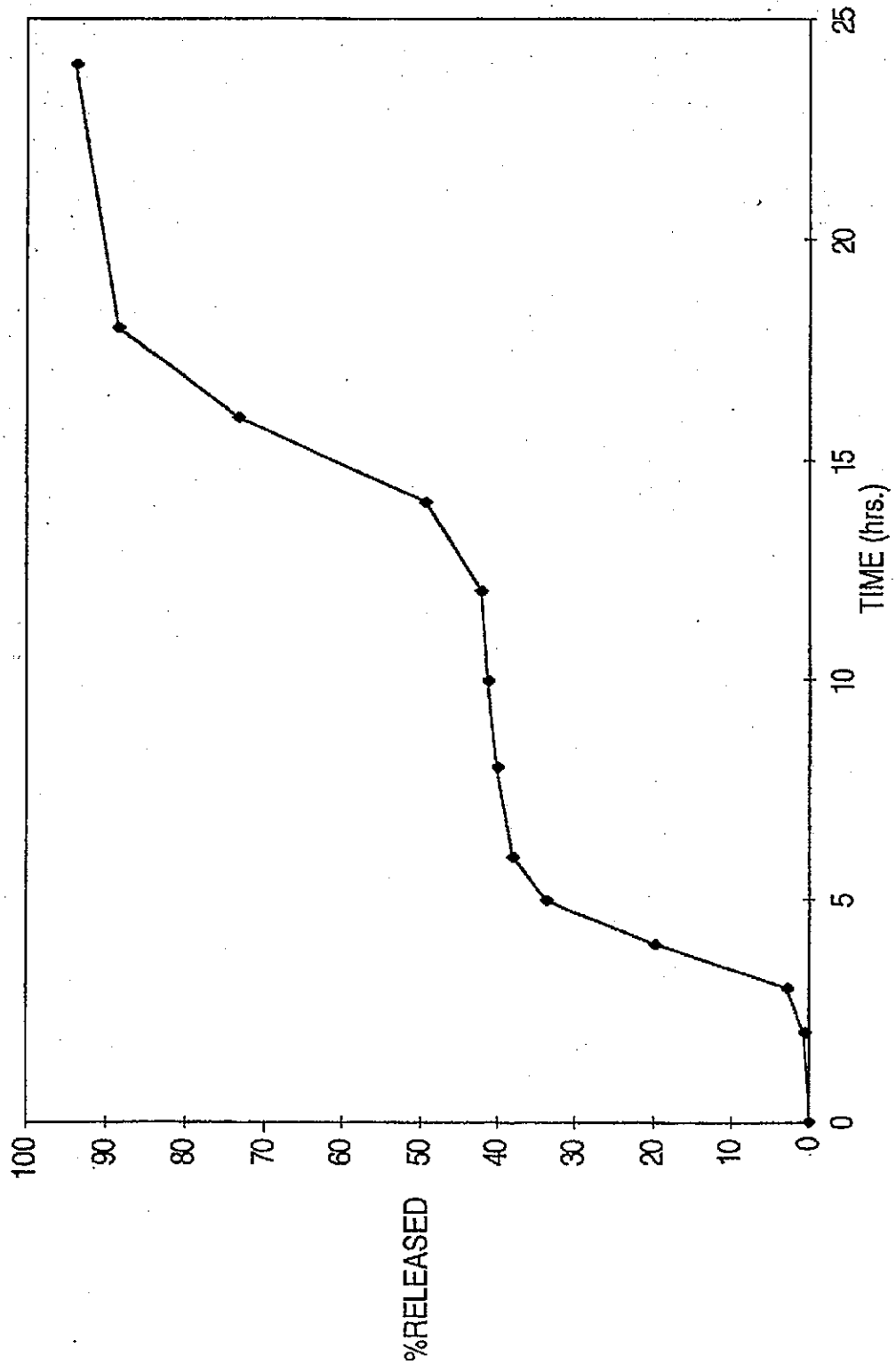


FIG. 4



SUSTAINED RELEASE DRUG DELIVERY SYSTEM SUITABLE FOR ORAL ADMINISTRATION

FIELD OF THE INVENTION

The present invention pertains to a drug delivery system suitable for oral administration that facilitates a two-step release of the active agent. A key aspect of the present invention is the discovery that a single orally administrable bead with multiply layered drug and polymer compartments can release the active agent in multiple phases to provide an immediate yet sustained drug delivery over a 24 hour period.

BACKGROUND OF THE INVENTION

Drug efficacy generally depends upon the ability of the drug to reach its target in sufficient quantity to maintain therapeutic levels for the desired time period. Orally administered drugs must overcome several obstacles to reach their desired targets. Before orally administered drugs enter the general circulation of the human body, they are absorbed into the capillaries and veins of the upper gastrointestinal tract and are transported by the portal vein to the liver. The pH and enzymatic activities found in gastrointestinal fluids may inactivate the drug or cause the drug to dissolve poorly. In addition, following their absorption in the intestine, orally administered drugs are often subject to a "first pass" clearance by the liver and excreted into bile or converted into pharmacologically inactive metabolites. Decreased bioavailability of orally administered drugs is a consequence of this first pass effect.

Orally administered drugs subject to the first pass effect generally exhibit non-linear pharmacokinetics. Until the liver's metabolic capacity has been exceeded, the amount of such drugs in the bloodstream is significantly lower than the amount administered. This metabolic elimination of the given dose results in reduced bioavailability. However, once the administered dose exceeds the liver's metabolic capacity, a significant increase in the drug concentration in the bloodstream may be obtained. The first pass phenomenon presents particular difficulties in the maintenance of therapeutic levels of an orally administered drug over an extended period such as 12 or 24 hours.

Drug delivery systems which have evolved with respect to orally administered drugs subject to the first pass effect include formulations capable of immediate drug release that are suitable for administration from 3–4 times daily, and formulations capable of immediate and sustained drug release that are suitable for once-daily administration. The second type of formulation is preferred because patient compliance with prescribed drug regimens involving once-daily administration is substantially higher than those involving multiple administrations. A sustained release formulation, however, may subject the patient to toxic drug levels over part of the dosing period and sub-therapeutic drug levels over other portions of the dosing period, if the drug release does not occur at appropriate time intervals. The maintenance of therapeutic levels of an orally administered drug over an extended period thus depends upon a drug delivery system capable of providing an appropriate release pattern.

Various drug delivery systems have been designed in attempts to ameliorate the first pass effect. U.S. Pat. No. 5,439,689 describes one such system designed to deliver the calcium antagonist diltiazem in a manner to maintain the drug in the bloodstream in therapeutic drug levels throughout the 24 hour period following oral administration. This

formulation accomplishes its dosing profile through the use of a blend of immediate drug release beads and delayed drug release beads. One disadvantage of this system is the relatively complicated manufacturing scheme. In contrast to a formulation comprising the blend of two types of drug release beads, a single bead formulation could be manufactured more simply. A single bead formulation would not require the time and effort required by the separate production of two types of drug release beads to prepare a final dosage form. Moreover, concerns regarding blending or double-filling homogeneity would be eliminated.

U.S. Pat. No. 4,894,240 describes an extended release drug delivery system in a single bead formulation. This system was also designed to deliver diltiazem in therapeutic drug levels over a 24 hour period following oral administration. However, subsequent tests demonstrated that the commercial product based on this patent's teachings was unable to provide optimal diltiazem blood levels over the 24 hour period following oral administration because of significant variances between peak and trough levels.

A valuable contribution to the art therefore would be the development of a drug delivery system in a single bead formulation suitable for oral administration that facilitates an immediate yet sustained release of the active agent over the 24 hour period following oral administration while minimizing the variance between peak and trough levels.

SUMMARY OF THE INVENTION

Accordingly, an objective of the present invention is a single orally administrable bead with multiply layered drug and polymer compartments that can release the active agent in multiple phases to provide an immediate yet sustained drug delivery over a 24 hour period with minimal variance between peak and trough levels. Another objective of the present invention is the control of the lag time between the initial and subsequent release of active agent. One other objective of the present invention is a comparative increase in active agent load (and thus drug density) above that achievable through a single bead formulation having a single layer of active agent.

The present invention accomplishes these objectives through a drug delivery system suitable for oral administration having a first drug compartment containing an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, optionally in association with pharmaceutically acceptable binder(s) or excipient(s); a first polymer compartment which substantially envelops the first drug compartment to form a first drug/polymer interface; a second drug compartment containing an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, optionally in association with pharmaceutically acceptable binder(s) or excipient(s), where the second drug compartment substantially envelops the first polymer compartment to form a second drug/polymer interface; and a second polymer compartment which substantially envelops the second drug compartment to form a third drug/polymer interface.

The active agent contained in the second drug compartment facilitates an initial release of active agent in an amount sufficient to achieve therapeutic levels at the appropriate target. The lag time and release rate of active agent from the second drug compartment is predominantly controlled by the second polymer compartment, which is composed mainly of one or more water insoluble polymers, one or more pH sensitive (i.e., enteric) polymers, and/or one or more water soluble polymers. Accordingly, the character of

the initial release phase may be altered by changing the polymer composition of the second polymer compartment.

Upon exposure of the drug delivery system to higher pHs, a pH sensitive polymer in the second polymer layer can dissolve. The dissolution of the pH sensitive polymer disrupts the polymer film and facilitates the complete release of the active agent from the second drug compartment. In turn, the first polymer compartment becomes exposed to the surrounding medium.

The active agent contained in the first drug compartment provides the sustained release of active agent in an amount sufficient to maintain therapeutic levels at the appropriate target throughout the 24 hour period following oral administration. When the second polymer and second drug compartments dissolve and/or detach from the drug delivery system, the first polymer compartment becomes exposed to the surrounding medium. The lag time and release rate of active agent from the first drug compartment is predominantly controlled by the first polymer compartment, which is composed mainly of one or more water insoluble polymers, one or more pH sensitive (i.e., enteric) polymers, and/or one or more water soluble polymers. Where a water soluble polymer is employed, the dissolution of the first polymer compartment facilitates the release of the active agent from the first drug compartment. Accordingly, the character of the sustained release phase may be altered by changing the polymer composition of the first polymer compartment.

DETAILED DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic drawing depicting a typical bead containing multiple layers of active drug and polymer materials. The release of the active agent from the second drug compartment is predominantly controlled by the second polymer compartment and provides an immediate release of active agent in an amount sufficient to achieve therapeutic levels at the appropriate target. The release of the active agent from the first drug compartment will likely occur after the dissolution and/or detachment of the second drug and second polymer compartments. In some instances, the release of active agent from the first drug compartment is significantly delayed by the presence of the second drug and second polymer compartments. The release profile of active agent from the first drug compartment is predominantly controlled by the first polymer compartment. The active agent contained in the first drug compartment provides the sustained release of active agent in an amount sufficient to maintain therapeutic levels at the appropriate target throughout the 24 hour period following oral administration.

FIG. 2 is a graph showing a typical in vitro drug release profile in simulated gastric fluid (SGF) (U.S. Pharmacopeia XXIII). Due to the presence of pH sensitive polymers in the second polymer compartment, the release of active agent from the first drug compartment is significantly minimized in an acidic environment. Any release from the first drug compartment in an acidic environment would likely result only from diffusion through both the first and second polymer compartments. Although the release of active agent from second drug compartment exhibits some pH sensitivity, the ratio of pH sensitive polymers and pH independent polymers in the second polymer compartment may be adjusted so that the release of active agent from the second drug compartment is independent of pH change in the acidic range. FIG. 2 illustrates the immediate release (e.g., approximately 40% of the total dose) of active agent which occurs between 2 to 6 hours after immersion into the simulated gastric fluid. The sustained release phase did not occur throughout the 24 hour time period in simulated gastric fluid.

FIG. 3 is a graph showing a typical in vitro drug release profile in simulated intestinal fluid (SIF) (as described in U.S. Pharmacopeia XXIII with the exception of the absence of pancreatin). Due to the pH sensitive nature of the second polymer compartment, the release of active agent from the second drug compartment (e.g., approximately 40% of total dose) occurs almost immediately, and ends within four hours, after immersion into the simulated intestinal fluid. With the dissolution and/or detachment of the second drug and second polymer compartments, the first polymer compartment becomes exposed to the simulated intestinal fluid. The first polymer compartment predominantly controls the release of active agent from the first drug compartment. FIG. 3 further illustrates that the sustained release phase (e.g., approximately 60% of the total dose) occurs between 6 to 15 hours after immersion into the simulated intestinal fluid.

FIG. 4 is a graph showing a typical in vitro drug release profile using an apparatus 3 assembly (U.S. Pharmacopeia XXIII) with a predetermined medium pH/time program. As such, test samples may be exposed sequentially to the following media for the specified time intervals: SGF (2 hours), pH 6 (1 hour), pH 6.5 (1 hour), pH 7 (1 hour), and SIF (19 hours). A stair-step release profile is depicted in this example, with the initial release phase and the subsequent release phase directed from the second drug compartment and the first drug compartment, respectively.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to a drug delivery system representing a single bead formulation suitable for oral administration that has multiple drug and polymer compartments which can release an active agent in multiple phases to provide an immediate yet sustained drug delivery over a 24 hour period with minimal variance between peak and trough levels.

The drug delivery system may also include a cosmetic coat compartment which substantially envelops the second polymer compartment to form a polymer/cosmetic coat interface. A cosmetic coat compartment can provide the drug delivery system with a desired glossy appearance or color.

In another embodiment, the drug delivery system also has one or more seal coat compartments. This seal coat compartment can exist at various locations of the drug delivery system, including the respective drug/polymer interfaces, the polymer/cosmetic coat interface, and substantially enveloping the second polymer compartment. In addition, a seal coat compartment may occur at multiple locations in the same drug delivery system. A seal coat compartment located at the first and third drug/polymer interfaces can minimize the solvent penetration or migration into the respective drug compartments during the coating process. A seal coat compartment located at the second drug/polymer interface or substantially enveloping the second polymer compartment can minimize the destruction or dissolution of the respective polymer compartments during production.

In one other embodiment, the first drug compartment substantially envelops a inert core. The inert core, typically a starch or sugar sphere, is a manufacturing alternative. In the pharmaceutical arts, well-known "drug layering" techniques exist to bind active agent on to the inert core (i.e., carrier) with an appropriate binding agent. The inert core typically has a diameter ranging from approximately 18 to 45 mesh and preferably within 35 to 40 mesh, if a high drug load is desired. The active agent may be layered on to the inert core using a conventional coating pan, a fluidized particle coater, or a rotogranulator.

In embodiments where an inert core is not employed, the first drug compartment may be prepared by incorporating suitable ingredients such as microcrystalline cellulose and the appropriate binders so that the active agent can be wet granulated, extruded, and spherinized to form spherical beads as described in the art.

The final single bead formulations may be filled into hard gelatin capsules to the desired weight to facilitate delivery of sufficient quantities of active agent to achieve or maintain therapeutic levels at the proper target. Final single bead formulations may also be applied to soft gelatin capsules or tablet dosage forms with the addition of proper excipients. For pediatric applications, the beads may be dispersed into a suitable liquid prior to administration.

The active agent of the present invention includes drugs that are subject to the first pass effect, and their pharmaceutically acceptable salts, pro-drug forms, metabolites, and derivatives. Various examples of such drugs include acetaminophen, aldosterone, alprenolol, amitryptyline, aspirin, beclomethasone diproprionate, bromocriptine, butorphanol tartrate, chlormethiazole, chlorpheniramine, chlorpromazine HCl, cimetidine, codeine, cortisone, cyclobenzamine HCl, desmethylimipramine, dextropropoxyphene, dihydroergotamine, diltiazem HCl, dobutamine HCl, domperidone, dopamine HCl, doxepin HCl, epinephrine, ergoloid mesylates, ergotamine tartrate, estradiol, ethinylestradiol, flunisolide, fluorouracil, flurazepam HCl, 5-fluoro-21-deoxyuridine, furosemide, glipizide, glyburide, glyceryl trinitrate, guanethidine sulfate, hydralazine HCl, imipramine HCl, indoramin, isoethorine HCl, isoethrine mesylate, isoprenaline, isoproterenol sulfate, isosorbide dinitrate, levallorphan tartrate, levodopa, lidocaine HCl, lignocaine, lorcainide, meperidine HCl, 6-mercaptopurine, metaproterenol sulfate, methoxamine HCl, methylphenidate, methylprednisolone, methyltestosterone mesylate, metoclopramide, metoprolol tartrate, morphine sulfate, nalbuphine HCl, naloxone HCl, neostigmine, nifedipine, nitrendipine, nitroglycerin, norepinephrine bitartrate, norethindrone, nortriptylene HCl, oxprenolol, oxyphenbutazone, penicillamine, pentazocine HCl, pentazocine lactate, pentobarbital, petnidine, phenacetin, phentolamine HCl, phentolamine mesylate, phenylephrine HCl, phenylephrine bitartrate, phenytoin, pindolal, prazosin, prednisone, progesterone, propoxyphene HCl, propoxyphene napsylate, propranolol HCl, quinidine, reserpine, ritodrine HCl, salicylamide, salbutamol, secobarbital, testosterone, terbutaline, timolol maleate, tolbutamide, and verapamil HCl.

In a preferred embodiment of the present invention, the active agent is diltiazem, or a pharmaceutically acceptable salt, diltiazem HCl. A further preferred embodiment is a drug delivery system containing diltiazem, which exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle method) according to U.S. Pharmacopeia XXIII at 37° C. in simulated gastric fluid at 100 rpm: (a) from about 0% to about 40% of total diltiazem is released after 3 hours of measurement in said apparatus; (b) from about 10% to about 50% of total diltiazem is released after 6 hours of measurement in said apparatus; (c) and no more than about 60% of total diltiazem is released after 12 hours of measurement in said apparatus.

In another preferred embodiment, the diltiazem exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated intestinal fluid at 100 rpm: (a) from about 20% to about 50% of total diltiazem is released after 3 hours of measurement in said apparatus; (b) from about 20% to about 60% of total diltiazem is released after 6 hours of measurement in said apparatus; (c) from about 35% to about 100% of total diltiazem is released after 12 hours of measurement in said apparatus; (d) no less than about 70% of total diltiazem is released after 24 hours of measurement in said apparatus.

In yet another preferred embodiment is a drug delivery system containing diltiazem, which exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated gastric fluid at 100 rpm: (a) from about 0% to about 40% of total diltiazem is released after 3 hours of measurement in said apparatus; (b) from about 10% to about 50% of total diltiazem is released after 6 hours of measurement in said apparatus; (c) no more than about 60% of total diltiazem is released after 12 hours of measurement in said apparatus; and also exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated intestinal fluid at 100 rpm: (a) from about 20% to about 50% of total diltiazem is released after 3 hours of measurement in said apparatus; (b) from about 20% to about 60% of total diltiazem is released after 6 hours of measurement in said apparatus; (c) from about 35% to about 100% of total diltiazem is released after 12 hours of measurement in said apparatus; (d) no less than about 70% of total diltiazem is released after 24 hours of measurement in said apparatus.

In one further embodiment, the amount of diltiazem contained in the first drug compartment and the amount of diltiazem contained in said second drug compartment is present in a weight/weight ratio from 4:1 to 1:4. Preferably, the amount of diltiazem contained in the first drug compartment and the amount of diltiazem contained in said second drug compartment is present in a weight/weight ratio of 3:2.

The first polymer compartment, or second polymer compartment, or both first and second polymer compartments, of the drug delivery system may contain suitable water insoluble polymers such as cellulose esters, cellulose ethers, and acrylic resins. Two examples of suitable acrylate polymer for use in the second polymer compartment are Eudragit RL™ and Eudragit RS™. With respect to the first polymer compartment, the acrylate polymers Eudragit RL™ and Eudragit RS™ are acceptable.

The first polymer compartment, or second polymer compartment, or both first and second polymer compartments, of the drug delivery system may contain suitable pH sensitive polymers such as hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, other cellulose ethers or esters, and acrylic resins. Two examples of suitable acrylate polymer for use in the second polymer compartment are Eudragit L™ and Eudragit S™. With respect to the first polymer compartment, the acrylate polymers Eudragit L™ and Eudragit S™ are acceptable.

The first polymer compartment, or second polymer compartment, or both first and second polymer compartments, of the drug delivery system may contain suitable water soluble polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, other cellulose ethers, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, starch, and hydroxyethyl cellulose.

Other excipients which can facilitate the manufacturing operation or final film quality may be included. These excipients include plasticizer, surfactant, hydrophobic anti-tackiness material, etc.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the

present invention to the fullest extent. The following examples are illustrative only, and not limiting of the remainder of the disclosure in any way whatsoever.

EXAMPLE ONE

An example of the composition of the first drug compartment is set forth in Table I.

TABLE I

Ingredient	% w/w range	% w/w example
diltiazem hydrochloride	70–100	90
binding agent(s)	0–30	9
surfactant	0–10	1

Either micronized or regular sized active raw material can be used to produce the single bead formulations. Both the aqueous and the organic solvent systems have been successfully evaluated and applied to this invention. Pharmaceutically acceptable solvents such as purified water, isopropyl alcohol, ethanol, etc., may be utilized. One or more binding agents may be incorporated to bind the active diltiazem blend onto the inert core. Examples of suitable binding agents include hydroxypropyl methylcellulose, ethyl cellulose, polyvinylpyrrolidone, polymerized acrylates, hydroxypropyl cellulose, hydroxyethyl cellulose, etc. Based upon the binding agent selected, the ratio between diltiazem and binding agent can vary widely.

The surfactant is employed, if necessary, to improve the texture of the drug compartments and/or properties of the final dosage form. Other pharmaceutical excipients such as glidant, anti-caking agent, lubricant, etc., may also be incorporated in the drug compartments to further improve the properties of the final product as described in the art.

The first polymer compartment provides approximately 6 to 12 hours lag time upon exposure to the surrounding medium before the sustained release phase of diltiazem from the first drug compartment. The polymer materials may include, but are not limited to, polymerized acrylates or copolymers of acrylic and methacrylic acid esters or esters of either monomer (hereinafter polymerized acrylates), methacrylic acid and methyl methacrylate copolymer (hereinafter methacrylic acid copolymer). These polymerized acrylates and methacrylic acid copolymers are commercially available from Rohm Tech Inc. under the tradenames Eudragit RS™, Eudragit RL™, Eudragit S™, and Eudragit L™. Other water insoluble polymers such as ethylcellulose, cellulose acetate, polydimethylsiloxane, etc., may also be employed to achieve the desired release characteristics. Water soluble polymers may also be incorporated in the polymer compartment. Examples of such polymers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, etc. Other pharmaceutically acceptable ingredients known in the art, such as water soluble pore formers, plasticizers, anti-caking (or anti-adherent) agents, lubricants, separating substances, anti-forming agents, surfactants, etc., may also be incorporated in the polymeric coating to achieve the desired properties or performance.

The first polymer compartment may be formed by various pharmaceutical coating technologies known in the art using suitable coating equipment such as pan coaters, fluidized particle coaters, and rotogranulators.

An example of the first polymer compartment composition is shown below:

TABLE II

Ingredient	% w/w range	% w/w example
Eudragit RS 100 ™	0–45	28
Eudragit RL 100 ™	0–30	5
Eudragit S 100 ™	0–45	28
Eudragit L 100 ™	0–30	5
Plasticizer	5–25	12
anti-caking agent	10–55	22

All the ingredients listed above may be dissolved or dispersed in the following solvent system, whether used alone or in combination: purified water, isopropyl alcohol, acetone, ethanol, etc. The weight of the dry solids applied to the first drug compartment may be in the range of about 20% to about 60% w/w, typically 40% w/w, of the total weight of the beads at this stage, i.e., the total weight of the inert core, if any, and the first drug and first polymer compartments. A sufficient quantity of the polymeric mixture is required to envelop the active core to ensure the desired lag time and release characteristics. The exact quantity may have to be adjusted carefully depending upon the formulation composition and the manufacturing processing conditions. The size of the first drug compartment dictates the bead surface area and therefore affects the thickness of the first polymer compartment if a fixed quantity of polymeric material is applied on to the first drug compartment.

The second drug compartment may consist of a similar formulation composition as that of the first drug compartment, which Table I illustrates. The ratio of diltiazem in the first drug compartment and the second drug compartment may be in the range of 4:1 w/w to 1:4 w/w, preferably 3:2 w/w.

The second polymer compartment provides 0 to 4 hours lag time upon exposure to the surrounding medium before the immediate release phase of diltiazem from the second drug compartment. The polymer materials may include, but are not limited to, polymerized acrylates or copolymers of acrylic and methacrylic acid esters or esters of either monomer (hereinafter polymerized acrylates), methacrylic acid and methyl methacrylate copolymer (hereinafter methyacrylic acid copolymer). These polymerized acrylates and methacrylic acid copolymers are commercially available from Rohm Tech Inc. under the tradenames Eudragit RS™, Eudragit RL™, Eudragit S™, and Eudragit L™. Enteric polymers which dissolve in weakly acidic, neutral or slightly alkaline medium may be incorporated to ensure the breakage of the polymer coating and thus expose the first polymer compartment when the dosage form reaches small intestine and loses all the diltiazem in the second drug compartment. Other water insoluble polymers such as ethylcellulose, cellulose acetate, polydimethylsiloxane, etc., may also be employed to achieve the desired release characteristics. Water soluble polymers may also be incorporated in the polymer coat. Examples of such polymers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, etc. Other pharmaceutically acceptable ingredients known in the art, such as water soluble pore formers, plasticizers, anti-caking (or anti-adherent) agents, lubricants, separating substances, anti-forming agents, etc., may also be incorporated in the polymeric coating to achieve the desired properties or performance.

The second polymer compartment may be formed by various pharmaceutical coating technologies known in the art using suitable coating equipment such as pan coaters, fluidized particle coaters, and rotogranulators.

An example of the second polymer compartment composition is shown below:

TABLE III

Ingredient	% w/w range	% w/w example
Eudragit RS 100 ™	0–30	10
Eudragit L 100 ™	0–50	30
Plasticizer	5–25	10
anti-caking agent	10–65	50

All the ingredients listed above may be dissolved or dispersed in the following solvent system, whether used alone or in combination: purified water, isopropyl alcohol, acetone, ethanol, etc. The weight of the dry solids applied to the second drug compartment core may be in the range of about 5% to about 30% w/w, typically 16% w/w, of the total weight of the beads at this stage, i.e., the total weight of the inert core, if any, the first drug and first polymer compartments, and the second drug and second polymer compartments.

An example of the in vitro dissolution profile of the drug delivery system containing diltiazem described above in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in 0.1N HCl at 100 rpm is shown below:

TABLE IV

Hours	% Released (Preferred Range)
3	0–40
6	0–50
24	25–60

An example of the in vitro dissolution profile of the drug delivery system containing diltiazem described above in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated gastric fluid (SGF) at 100 rpm is shown below:

TABLE V

Hours	% Released (Preferred Range)
3	0–40
6	0–50
24	25–60

An example of the in vitro dissolution profile of the drug delivery system containing diltiazem described above in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated intestinal fluid (SIF) at 100 rpm is shown below:

TABLE VI

Hours	% Released (Preferred Range)
3	20–50
6	20–60
12	35–100
24	70–100

An example of the in vitro dissolution profile of the drug delivery system containing diltiazem described above in a type 3 bio-disk method according to U.S. Pharmacopeia XXIII at 37° C. in a predetermined pH/time program at 100 rpm is shown below. An example of the predetermined pH/time program is as follows: SGF-2 hours; pH 6-1 hour; pH 6.5-1 hour; pH 7-1 hour; and SIF-19 hours.

TABLE VII

Hours	% Released (Preferred Range)
3	0–40
6	20–60
12	30–100
24	80–100

Those skilled in the art will find it apparent that various modifications and variations can be made to the formulations of this invention. Thus, the present invention is intended to cover such modifications and variations, provided they come within the scope of the appended claims and their equivalents.

The disclosure of all publications cited above are expressly incorporated herein by reference in their entireties to the same extent as if each were incorporated by reference individually.

What is claimed is:

1. A single bead drug delivery system suitable for oral administration comprising:

a) a first drug compartment containing an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, optionally in association with a pharmaceutically acceptable binder or excipient;

b) a first polymer compartment which substantially envelops said first drug compartment to form a first drug/polymer interface;

c) a second drug compartment containing an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, optionally in association with a pharmaceutically acceptable binder or excipient, wherein said second drug compartment substantially envelops said first polymer compartment to form a second drug/polymer interface;

d) a second polymer compartment which substantially envelops said second drug compartment to form a third drug/polymer interface; and

wherein said single bead drug delivery system can release said active agent in multiple phases.

2. The drug delivery system of claim 1, which further comprises:

e) a cosmetic coat compartment which substantially envelops said second polymer compartment to form a polymer/cosmetic coat interface.

3. The drug delivery system of claim 1, which further comprises a seal coat compartment at said first drug/polymer interface.

4. The drug delivery system of claim 1, which further comprises a seal coat compartment at said second drug/polymer interface.

5. The drug delivery system of claim 1, which further comprises a seal coat compartment at said third drug/polymer interface.

6. The drug delivery system of claim 1, which further comprises a seal coat compartment that substantially envelops said second polymer compartment.

7. The drug delivery system of claim 2, which further comprises a seal coat compartment at said polymer/cosmetic coat interface.

8. The drug delivery system of claim 1, which further comprises a first seal coat compartment at said first drug/polymer interface and a second seal coat compartment at said third drug/polymer interface.

9. The drug delivery system of claim 1, which further comprises a first seal coat compartment at said second drug/polymer interface and a second seal coat compartment that substantially envelops said second polymer compartment.

10. The drug delivery system of claim 2, which further comprises a first seal coat compartment at said second drug/polymer interface and a second seal coat compartment at said polymer/cosmetic coat interface.

11. The drug delivery system of claim 1, wherein said first drug compartment substantially envelops an inert core.

12. The drug delivery system of claim 1, wherein said active agent is diltiazem, or a pharmaceutically acceptable salt thereof.

13. The drug delivery system of claim 12, wherein said diltiazem exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated gastric fluid at 100 rpm:

a) from about 0% to about 40% of total diltiazem is released after 3 hours of measurement in said apparatus;

b) from about 10% to about 50% of total diltiazem is released after 6 hours of measurement in said apparatus; and

c) no more than about 60% of total diltiazem is released after 12 hours of measurement in said apparatus.

14. The drug delivery system of claim 12, wherein said diltiazem exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated intestinal fluid at 100 rpm:

a) from about 20% to about 50% of total diltiazem is released after 3 hours of measurement in said apparatus;

b) from about 20% to about 60% of total diltiazem is released after 6 hours of measurement in said apparatus;

c) from about 35% to about 100% of total diltiazem is released after 12 hours of measurement in said apparatus; and

d) no less than about 70% of total diltiazem is released after 24 hours of measurement in said apparatus.

15. The drug delivery system of claim 12, wherein said diltiazem exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated gastric fluid at 100 rpm:

a) from about 0% to about 40% of total diltiazem is released after 3 hours of measurement in said apparatus;

b) from about 10% to about 50% of total diltiazem is released after 6 hours of measurement in said apparatus; and

c) no more than about 60% of total diltiazem is released after 12 hours of measurement in said apparatus; and

wherein said diltiazem exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXIII at 37° C. in simulated intestinal fluid at 100 rpm:

a) from about 20% to about 50% of total diltiazem is released after 3 hours of measurement in said apparatus;

b) from about 20% to about 60% of total diltiazem is released after 6 hours of measurement in said apparatus;

c) from about 35% to about 100% of total diltiazem is released after 12 hours of measurement in said apparatus; and

d) no less than about 70% of total diltiazem is released after 24 hours of measurement in said apparatus.

16. The drug delivery system of claim 12, wherein the amount of diltiazem contained in said first drug compartment and the amount of diltiazem contained in said second drug compartment is present in a weight/weight ratio from 4:1 to 1:4.

17. The drug delivery system of claim 12, wherein the amount of diltiazem contained in said first drug compartment and the amount of diltiazem contained in said second drug compartment is present in a weight/weight ratio of 3:2.

18. The drug delivery system of claim 1, wherein said first polymer compartment, or second polymer compartment, or both first and second polymer compartments, contains one or more water insoluble polymer(s) selected from the group consisting of cellulose esters, cellulose ethers, and acrylic resins.

19. The drug delivery system of claim 1, wherein said first polymer compartment, or second polymer compartment, or both first and second polymer compartments, contains one or more pH sensitive polymer(s) selected from the group consisting of hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, other cellulose ethers or esters, and acrylic resins.

20. The drug delivery system of claim 1, wherein said first polymer compartment, or second polymer compartment, or both first and second polymer compartments, contains one or more water soluble polymer(s) selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, other cellulose ethers, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, starch, and hydroxyethyl cellulose.

* * * * *

Exhibit 62

REDACTED

Exhibit 63

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(1) Amy Hulina (3) _____

(2) Robert Boswell, Jr. (4) _____

Date of Interview 7/30/97

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative)...

Exhibit shown or demonstration conducted: ☐ Yes ☒ No If yes, brief description: _____

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: 6, 9 and 10

Identification of prior art discussed: Upton et al. (5,506,270)

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Agreed to amend claims 9 and 10 to depend from claim 1 to avoid reference over Upton which discloses extended release venlafaxine at col 3, lines 25-27

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM PTOL-413 (REV.1-96)

WYETH 002-000850

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

A complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

* * * * *

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for response to Office action as specified in §§ 1.111, 1.135. (35 U.S.C.132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and filed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desireable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

*U.S. GPO: 1998-404-496/40513

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN	D AHP-95011

EXAMINER

15M2/0805

RONALD W. ALICE
AMERICAN HOME PRODUCTS CORPORATION
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

ART UNIT	PAPER NUMBER
1501	31a

HULINA, A

DATE MAILED 08/05/97 8:427

NOTICE OF ALLOWABILITY

PART I.

1. [X] This communication is responsive to 7/30/97
2. [X] All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. [X] The allowed claims are 1-5, 7-10
4. [ ] The drawings filed on _____ are acceptable.
5. [ ] Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received, [_] not been received, [_] been filed in parent application Serial No. _____ filed on _____
6. [X] Note the attached Examiner's Amendment.
7. [X] Note the attached Examiner Interview Summary Record, PTOL-413.
8. [X] Note the attached Examiner's Statement of Reasons for Allowance.
9. [X] Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. [X] Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. [ ] Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. [ ] APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. [ ] Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. [ ] The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. [ ] Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. [ ] Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:
- [X] Examiner's Amendment
- [X] Examiner Interview Summary Record, PTOL-413
- [X] Reasons for Allowance
- [X] Notice of References Cited, PTO-892
- [X] Information Disclosure Citation, PTO-1449
- [ ] Notice of Informal Application, PTO-152
- [ ] Notice re Patent Drawings, PTO-948
- [ ] Listing of Bonded Draftsmen
- [ ] Other

Amy Hulina
Primary Examiner
Group 1500

WYETH 002-000852

PTOL-37 (REV. 4-89) *

USCOMM-DC 89-0789

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-5,7-10, drawn to a composition and method, classified in class 424, subclass 461.

   II. Claim 6, drawn to a film coating, classified in class 427, subclass 3.

2. The inventions are distinct, each from the other because of the following reasons: Inventions I and II are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because claim 1 does not require the specific ethyl cellulose and hydroxypropylmethylcellulose in the particular amounts recited in claim 6. The subcombination has separate utility such as a film coating.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Robert Boswell, Jr. on 7/30/97 a provisional election was made with traverse to prosecute the invention of I, claims 1-5,7-10. Affirmation of this election must be made by applicant in responding to this Office action. Claim 6 is withdrawn

from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Robert Boswell, Jr. on 7/30/97.

6. The application has been amended as follows:

7. Claim 6 has been cancelled.

8. In claim 9, line 3, after "thereof", "an" has been changed to "the"; in line 4, after "formulation", ---of claim 1--- has been inserted; in line 4, after "formulation", "that" has been changed to "which".

9. In claim 10, line 3, after "thereof", "an" has been changed to "the"; in line 4, after "formulation", ---of claim 1--- has been inserted; in line 4, after "formulation", "that" has been changed to "which". The following is an examiner's statement of reasons for allowance: The prior art does not teach or suggest the specific extended release claim formulation according to claim 1.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy Hulina whose telephone number is (703) 308-2974.

Amy Hulina
Primary Examiner
Group 1500

AH

August 4, 1997

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP–APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	08/821,137	1501	3
	APPLICANT(S) Sherman		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
X	A	5506270	4/96	Upton et al	514	730	
X	B	5532244	7/96	Wong et al	514	255	
X	C	5530013	6/96	Husbands et al	514	330	
X	D	4535186	8/85	Husbands et al	564	336	
X	E	4761501	8/88	Husbands et al	564	167	•
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M			NONE					
	N								
	O								
	P		✓						
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	
S	
T	
U	

EXAMINER	DATE
Amy Hulse	7/30/97

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

WYETH 002-000856

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN D	AHP-95011

75F1/0203

RONALD W. ALICE
AMERICAN HOME PRODUCTS CORPORATION
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

EXAMINER	
HULINA, A	
ART UNIT	PAPER NUMBER
1501	05

DATE MAILED: 02/03/98

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☑ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 08/05/97 of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

DIRECT ANY INQUIRIES TO :
PUBLISHING DIVISION
MARCIA CAMPBELL-JONES
(703) 305-8190
OR
PRISCILLA FULLER
(703) 305-8203

WYETH 002-000911

PTO-1432 (REV. 5-83)

Exhibit 64

PW 1006163

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

May 28, 2003

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

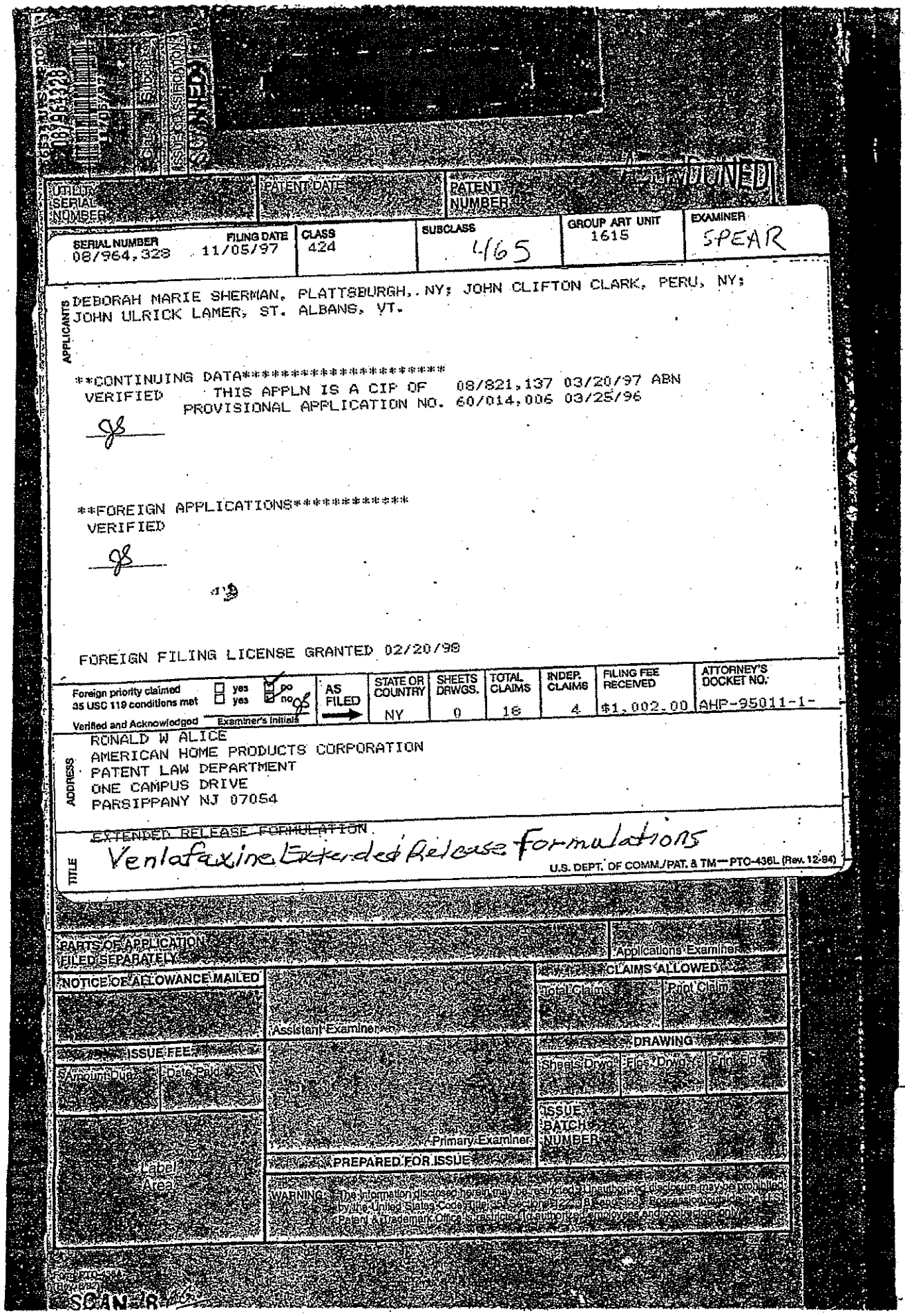
APPLICATION NUMBER: *08/964,328*
FILING DATE: *November 05, 1997*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

WYETH 002-000563



08/964,328
CLASS 424
SUBCLASS
ISSUE CLASSIFICATION
SCANNED

UTILITY SERIAL NUMBER | PATENT DATE | PATENT NUMBER

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/964,328	11/05/97	424	465	1615	SPEAR

APPLICANTS
DEBORAH MARIE SHERMAN, PLATTSBURGH, NY; JOHN CLIFTON CLARK, PERU, NY;
JOHN ULRICK LAMER, ST. ALBANS, VT.

CONTINUING DATA********
VERIFIED THIS APPLN IS A CIP OF 08/821,137 03/20/97 ABN
PROVISIONAL APPLICATION NO. 60/014,006 03/25/96

gs

FOREIGN APPLICATIONS********
VERIFIED

gs

FOREIGN FILING LICENSE GRANTED 02/20/98

Foreign priority claimed 35 USC 119 conditions met Verified and Acknowledged Examiner's Initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
☐ yes ☐ yes ☑ no gs	→	NY	0	16	4	$1,002.00	AHP-95011-1-

ADDRESS
RONALD W ALICE
AMERICAN HOME PRODUCTS CORPORATION
PATENT LAW DEPARTMENT
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

TITLE
~~EXTENDED RELEASE FORMULATION~~
Venlafaxine Extended Release Formulations

U.S. DEPT. OF COMM./PAT. & TM — PTO-436L (Rev. 12-94)

PARTS OF APPLICATION FILED SEPARATELY | Group Art Unit | Applications Examiner

NOTICE OF ALLOWANCE MAILED | Assistant Examiner | CLAIMS ALLOWED: Total Claims | Print Claim

ISSUE FEE: Amount Due | Date Paid | DRAWING: Sheets Drwg. | Figs. Drwg. | Print Fig.

Label Area | Primary Examiner | ISSUE BATCH NUMBER

PREPARED FOR ISSUE

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436L (Rev. 8/92)

SCANNED

WYETH 002-000564

CERTIFICATE OF MAILING BY "E... ...SS MAIL"

"EXPRESS MAIL" MAILING LABEL NUMBER EM474051411US

DATE OF DEPOSIT November 5, 1997

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE BY "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231

Arthur G. Seifert

(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Arthur G. Seifert

(SIGNATURE OF PERSON MAILING PAPER OR FEE)

U.S. ...PARTMENT OF COMMERCE
Patent and Trademark Office

Address Only: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

66534 U.S. PTO
08/964328
11/05/97

Case Docket No. AHP-95011-1-C1
PATENT

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of

Inventor: Deborah M. Sherman, John Clifton Clark, John Ulrick Lamar

For: Extended Release Formulation

Enclosed are:

☐ _____sheets of drawing.

☐ An assignment of the invention to_____

☐ A certified copy of a _____application.

☐ Associate power of attorney.

CLAIMS AS FILED				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) BASIC FEE $790.00
TOTAL CLAIMS	18 -20=	0	x $22.00	0.00
INDEPENDENT CLAIMS	5 -3=	2	x $82.00	164.00
MULTIPLE DEPENDENT CLAIMS	0	0	$270.00	0.00
			TOTAL FILING FEE →	954.00

☒ Please charge my Deposit Account No. 01-1425 in the amount of $ 954.00 Two additional copies of this sheet are enclosed.

☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of the application to Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

☐ A check in the amount of _____ to cover the filing fee is enclosed.

☒ This application is a continuation-in-part under 37 CFR 1.53(b) of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.

Arthur G. Seifert
Reg. No. 28,040

WYETH 002-000565

FORM PO-1082 (11-69)

USCOMM-DC 60424-P69

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"EXPRESS MAIL" MAILING LABEL NUMBER 4051411US
DATE OF DEPOSIT November 5, 1997

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE BY "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231

Arthur G. Seifert
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Arthur G. Seifert
(SIGNATURE OF PERSON MAILING PAPER OR FEE)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address Only: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Case Docket No. AHP-95011-1-C1
PATENT

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of

Inventor: Deborah M. Sherman, John Clifton Clark, John Ulrick Lamar

For: Extended Release Formulation

Enclosed are:

☐ _____ sheets of drawing.

☐ An assignment of the invention to _____

☐ A certified copy of a _____ application.

☐ Associate power of attorney.

CLAIMS AS FILED				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) BASIC FEE $790.00
TOTAL CLAIMS	18 -20=	0	x $22.00	0.00
INDEPENDENT CLAIMS	5 -3=	2	x $82.00	164.00
MULTIPLE DEPENDENT CLAIMS	0	0	$270.00	0.00
			TOTAL FILING FEE →	954.00

☒ Please charge my Deposit Account No. 01-1425 in the amount of $ 954.00. Two additional copies of this sheet are enclosed.

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☒ This application is a continuation-in-part under 37 CFR 1.53(b) of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.

Arthur G. Seifert
Reg. No. 28,040

FORM PO-1082 (11-89)

USCOMM-DC 60424-P89

M2789 L (5/95)

66534 U.S. PTO
08/964328
11/05/97

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

01/15/1998 MGORDON 00000021 DAH:011425 08964328
01 FC:101 790.00 CH
02 FC:102 82.00 CH

PTO-1556
(5/87)

ABSTRACT

EXTENDED RELEASE FORMULATION

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets.

EXTENDED RELEASE FORMULATION

This application is a continuation-in-part of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.

Background of the Invention

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/antiinflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, chopped into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. Gelatin capsules are filled with the film-coated spheroids in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a gelatin capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose

wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day , in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours.

Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w) , with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent

venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropyl methylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropyl methylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55°C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropyl methylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone,

methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride–microcrystalline cellulose mix made production of spheroids practical.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

Example 1.

VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropyl methylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into hard gelatin capsules conventionally.

Example 2.

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example 3.

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example 4.

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethyl cellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5 % (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6 % (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide,

after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

Table 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into hard gelatin capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

[Text continues with Table 2 on next page]

Table 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate

release tablets given 12 hours apart. The peak level of venlafaxine from (ER) , somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

Table 3.

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 µL of a stock internal standard solution (150 µg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50µL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 µL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 µ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Thus, the desired dissolution rate of a sustained release dosage form of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

3. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

4. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

5. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

6. A composition according to claim 2 wherein the film coating comprises 6- 8% by weight of total weight.

7. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

8. A composition according to claim 2 wherein film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

9. A film coating composition according to claim 7 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

10. A film coating composition according to claim 7 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

11. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

12. An extended release formulation of venlafaxine hydrochloride according to claim 7 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

13. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

14. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Sub A4 15. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 6% to 40% venlafaxine hydrochloride by weight, about 50% to about 940% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

16. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 15 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Add #4

17. An extended release formulation according to claim 14 wherein the spheroids are composed of about 8.25% by weight of venlafaxine hydrochloride and about 91.75% by weight of microcrystalline cellulose, with a coating of from 3 to 5 % by weight of the total weight.

18. An extended release formulation according to claim 14 wherein the spheroids are composed of about 16.5% by weight of venlafaxine hydrochloride and about 83.5% by weight of microcrystalline cellulose, with a coating of from 4 to 6 % by weight of the total weight.

Add #5

Exhibit 65

IN 992372

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April 28, 2003

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By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. PHILLIPS
Certifying Officer

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to Claim 1 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

3. An extended release formulation according to Claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to Claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to Claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to Claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1 % to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose,

7. An extended release formulation according to Claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose

9. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to Claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55

T 0210

8	55-80
12	65-90
24	>80

12. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

13. ~~A composition~~ An extended release formulation according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. ~~A composition~~ An extended release formulation according to claim 2 wherein the film coating comprises 6-8% by weight of total weight.

15. ~~A composition~~ An extended release formulation according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. ~~A composition~~ An extended release formulation according to claim 2 wherein the film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

17. A film coating composition according to Claim 2 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. A film coating composition according to Claim 2 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropylmethylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

20. An extended release formulation of venlafaxine hydrochloride according to Claim 2 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

21. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Office Action Summary

Application No.	Applicant(s)
09/488,629	SHERMAN, ET AL.
Examiner	**Group Art Unit**
JAMES M. SPEAR	1615

☒ Responsive to communication(s) filed on *Jan 20, 2000*

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-22* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *21 and 22* is/are allowed.

☒ Claim(s) *1, 12, 18, and 19* is/are rejected.

☒ Claim(s) *2-11, 13-17, and 20* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2,5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 18 and 19 contain the trademark/trade name HYDROXYPROPYLMETHYLCELLULOSE TYPE 2208 and TYPE 2910 and ETHYLCELLULOSE TYPE HG 2834. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to

identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a hydroxyalkylcellulose (hydroxypropylmethylcellulose) and ethylcellulose and, accordingly, the identification/description is indefinite. It is unclear as to what the type terminology is indicative of and how the various compounds differ based on the number notation.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al U.S. 4,138,475 in view of Wong et al U.S. 5,552,429.

McAinsh et al shows a hard gelatin capsule comprised of spheroids coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The active agent propranolol is blended with microcrystalline cellulose to formulate the core spheroid. See Abstract, example and claim 1. The reference does not show venlafaxine. Wong et al is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al in the McAinsh et al capsule with a reasonable expectation of success would have been obvious to one of ordinary skill in the art.

Given the teachings of the prior art it would be reasonable to expect that propranolol common to both McAinsh et al and Wong et al could be combined with venlafaxine in a sustained release dosage form to increase patient compliance when the need arises to administer both drugs. The motivation being a desire to obtain optimum drug efficacy over a prolonged period of time while reducing the total number of dosages required.

Claims 2-11, 13-17 and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 1, 12, 18 and 19 are rejected.

Claims 21 and 22 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308-2457. The examiner can normally be reached on Monday thru Friday from 6:30 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for this Group is (703) 305-3592 or 308-4556.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**thurman.page@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

James M. Spear

January 3, 2001

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

Notice of References Cited

Application No.	Applicant
09/488,629	SHERMAN, ET AL.

Examiner	Group Art Unit	Page 1 of 1
JAMES M. SPEAR	1615	

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A	4,138,475	2/1979	McAinsh, et al	424	19
B	5,552,429	9/1996	WONG, ET AL.	514	415
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
U		
V		
W		
X		

Exhibit 66

IW 992376

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 28, 2003

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *09/884,412*
FILING DATE: *June 19, 2001*
PATENT NUMBER: *6,419,958*
ISSUE DATE: *July 16, 2002*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. JACKSON
Certifying Officer

WYETH 002-000450

Office Action Summary

Application No.	Applicant(s)
09/884,412	SHERMAN, ET AL
Examiner	**Art Unit**
JAMES M. SPEAR	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 19, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 23, and 24* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 23, and 24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23 and 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20 and 21 of U.S. Patent No. 6,274,171. Although the conflicting claims are not identical, they are not patentably distinct from each other because while the claims of the patent require an encapsulated dosage form, to administer the extended release formulation in an unencapsulated form would have been obvious to one of ordinary skill in the art. The encapsulation is a means for containing the extended release dosage form. Since the capsule dose not provide the means for extended release, it would be reasonable to expect one skilled in the art would modify the dosage form and administer the venlafaxine spheroids as unencapsulated dosages. The motivation being to optimize patient compliance and convenience of administration. Individuals having difficulty swallowing capsules would be more apt to comply with a dosage regimen when the formulation is unencapsulated and therefore easier to swallow.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al US 4,138,475 in view of Wong et al US 5,552,429.

McAinsh et al shows a hard gelatin capsule comprised of spheroids coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The active agent propranolol is blended with microcrystalline cellulose to form a core spheroid. See Abstract, the example and claim 1. The sustained release results from the coating applied to the individual spheroids. The reference does not show venlafaxine. Wong et al is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al in the McAinsh et al capsule, coated for sustained release, with a reasonable expectation of success would have been obvious to one of ordinary skill in the art. It would be reasonable to expect that propranolol common to both McAinsh et al and Wong et al could be combined with venlafaxine in a sustained release dosage form to increase patient

compliance when the need arises to administer both drugs. The resulting combination dosage form would provide optimum drug efficacy over a prolonged period of time while reducing the total number of dosages required.

Claims 1, 23 and 24 are rejected. Claims 2-22 have been canceled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308 2457. The examiner can normally be reached on Monday thru Friday from 6:30 AM to 3 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305 3592 or 308 4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308 1235.

James M. Spear January 13, 2002

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

Docket No: AHP-95011 D1
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	Deborah M. SHERMAN, et al		
Serial No.:	09/884,412	Group Art No.:	1615
Filed:	June 19, 2001	Examiner:	James M. Spear
For:	EXTENDED RELEASE FORMULATION		
Confirmation No.:	2298		
Customer Number:	25291		

FAX RECEIVED
APR 16 2002
GROUP 1600

Commissioner for Patents
Washington, DC 20231

OFFICIAL

Sir:

AMENDMENT TRANSMITTAL LETTER

1. Enclosed please find the following documents for the above-identified application:

a. Response to Office Action mailed on January 14, 2002

b. Terminal Disclaimer

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper and the documents referred to as enclosed therein are being facsimile transmitted with the United States Patent Office at 703-305-9592 on the date written below

April 15, 2002
Date

Rebecca Barrett
Rebecca Barrett

Docket No: AHP-95011 D1
Patent

2. Fee calculation

CLAIMS AS AMENDED					
(1) FOR	(2) CLAIMS REMAINING AFTER AMENDMENT	(3) HIGHEST NUMBER PAID FOR	(4) NUMBER EXTRA	x RATE	(5) ADDITIONAL FEE
TOTAL CLAIMS	6	20	0	x $ 18.00	0.00
INDEPENDENT CLAIMS	6	3	3	x $ 84.00	252.00
MULTIPLE DEPENDENCY FEE				$ 280.00	
			Total Amendment Fee:		$252.00

Fee for filing terminal disclaimer under 37 C.F.R. 1.20(d) $110.00

☒ Please charge Deposit Account No. 01-1425 for: $252.00

The Commissioner is hereby authorized to charge any additional fees required by this paper, including the enclosed documents, and during the entire pendency of this application and to credit any excess amounts paid to Deposit Account No. 01-1425. A copy of this letter is enclosed for use by the Deposit Account Branch.

Respectfully submitted,

Rebecca Barrett

Rebecca R. Barrett
Attorney for Applicants
Reg. No. 35,152

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2646

B

Docket No: AHP-95011 D1
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	Deborah M. SHERMAN, et al.		
Serial No.:	09/884,412	Group No.:	1615
Filed:	June 19, 2001	Examiner:	James M. Spear
For:	EXTENDED RELEASE FORMULATION		
Confirmation No.:	2298		
Customer Number:	25291		

Commissioner for Patents
Washington, DC 20231

AMENDMENT

This is in response to the Office Action issued in connection with this case on January 14, 2002.

Please amend the application as follows:

In the Claims

Please cancel Claim 1, without prejudice.

Please add the following new claims:

--25. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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26. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

27. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

28. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. --

Remarks

Claims 1, 23 and 24 were pending in this case. Claims 1, 23 and 24 were rejected. Claims 25-28 were added to more fully claim Applicants' invention. No new matter was added by these claims.

Claims 23 and 24 were rejected under the doctrine of obviousness type double patenting as being unpatentable over Claims 20 and 21 of U.S. 6,274,171. The Examiner states that it would be reasonable to expect one skilled in the art to modify the dosage form and administer the venlafaxine spheroids as unencapsulated dosages. Applicants disagree with the Examiner's characterization of the invention

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and note that the claims are not limited simply to unencapsulated spheroids. However, to facilitate prosecution, Applicants have submitted herewith a terminal disclaimer, disclaiming any portion of this application beyond the term of the '171 patent.

Claim 1 was rejected under 35 U.S.C. §103. Claim 1 has been cancelled, without prejudice, making this rejection moot.

In view of the foregoing, Applicants respectfully maintain that Claims 23-28 are in condition ready for allowance and request an early and favorable Notice of Allowance.

Rebecca R. Barrett

Rebecca R. Barrett

Reg. No. 35,152

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2846

B

Docket No: AHP-95011 D1
Patent

Version with Markings to Show Changes Made

Amend the application as follows:

Please cancel Claim 1, without prejudice.

Please add the following new claims:

--25. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

26. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

27. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

28. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of

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venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. --

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Notice of Allowability

Application No.	Applicant(s)
09/884,412	SHERMAN, ET AL
Examiner	**Art Unit**
JAMES M. SPEAR	1615

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *THE AMENDMENT AND DISCLAIMER FILED APRIL 15, 2002*.
2. ☒ The allowed claim(s) is/are *23-28*.
3. ☐ The drawings filed on _____ are acceptable as formal drawings.
4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____.
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   *Certified copies not received: _____.
5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. _____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.
8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

1 ☐ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☐ Examiner's Statement of Reasons for Allowance
9 ☐ Other

James M. Spear

JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

Exhibit 67

IW 992374

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 24, 2003

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *09/950,965*
FILING DATE: *September 12, 2001*
PATENT NUMBER: *6,403,120*
ISSUE DATE: *June 11, 2002*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WOODSON
Certifying Officer

WYETH 002-000344

Office Action Summary	Application No. 09/950,965	Applicant(s) SHERMAN, ET AL
	Examiner JAMES M. SPEAR	Art Unit 1615

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 12, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 23-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *23* is/are allowed.

6) ☒ Claim(s) *1* is/are rejected.

7) ☒ Claim(s) *24-34* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-34 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are dependent claims which depend on a method, however claims 24 and 25 depend on claim 1 which is a product/composition claim..

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al US 4,138,475 in view of Wong et al US 5,552,429.

McAinsh et al shows a hard gelatin capsule comprised of spheroids coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The active agent propranolol is blended with microcrystalline cellulose to formulate the core spheroid. See Abstract, example and claim 1. The reference does not show venlafaxine. Wong et al is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al in the McAinsh et al capsule with a reasonable expectation of success would have been obvious to one of ordinary skill in the art. It would be reasonable to expect that propranolol common to both McAinsh et al and Wong et al could be combined with venlafaxine in the McAinsh sustained release dosage form to increase patient compliance when the need arises to administer both drugs. The motivation being a desire to obtain

optimum drug efficacy over a prolonged period of time while reducing the total number of dosages required. It is also reasonable to expect that one may choose to use the same sustained release formulation for either drug alone in a single dosage form for those times when only venlafaxine or propranolol is required to be administered as a sustained/extended release formulation. The goal being to obtain optimum release profiles.

Claim 23 is allowed.

Claims 2-22 have been canceled. Claims 24-34 are objected to. Claim 1 is rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308 2457. The examiner can normally be reached on Monday thru Friday from 6:30 AM to 3 PM .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305 3592 or 308 4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308 1235.

James Spear

December 3, 2001

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

#5/B

Docket No: AHP-95011 C1
Patent

3/16/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of:	Deborah M. SHERMAN, John C. CLARK, John U. LAMER, Stephen A. WHITE		
Serial No.:	09/950,965	Group No.:	1615
Filed:	September 12, 2001	Examiner:	James M. Spear
For:	Extended Release Formulation		
Confirmation No.:	2886		
Customer Number:	25291		

Commissioner for Patents
Washington, DC 20231

AMENDMENT UNDER 37 C.F.R. §1.111

Sir:

This is in response to the Office Action issued in connection with this case on December 5, 2001. The Office Action has been carefully reviewed and the following response prepared. Please amend the application as follows:

In the Claims:

2 ~~24.~~ (Amended) The method of Claim ~~23~~ 1 wherein the extended release formulation is encapsulated.

3 ~~25.~~ (Amended) The method of Claim ~~23~~ 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose.

Please add the following new claims:

13 ~~35.~~ The method of Claim ~~23~~ 1 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid.

14 ~~36.~~ The method of Claim ~~23~~ 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid.

Please cancel Claim 1, without prejudice.

Remarks

Claims 1 and 23-34 were pending in this application. Claim 1 was cancelled, without prejudice. New Claims 35 and 36 were added to more fully claim subject matter of the claimed invention. Claim 1 was rejected. Claims 24-34 were objected to. Applicants appreciate the Examiner's indication that Claim 23 is allowed.

Claims 24-34 were objected to as being of inproper dependent form. Applicants have amended the dependencies of claims 24 and 25 to depend from Claim 23. Claims 24-34 now properly depend, directly or indirectly, from Claim 23. Accordingly the dependencies have been corrected and this objection should be withdrawn.

Claims 35 and 36 were added to more fully claim the subject matter of the invention. No new matter was added by this amendment.

Claim 1 was rejected under §103(a). To facilitate prosecution of this application, Claim 1 was cancelled, without prejudice, making this rejection moot.

In view of the foregoing, Applicants respectfully maintain that Claims 23-36 are in condition ready for allowance and respectfully request an early and favorable Notice of Allowance.

Respectfully submitted,

Rebecca L. Barrett

Rebecca R. Barrett
Reg. No. 35, 152
Attorney for Applicants

Dated: March 5, 2002
Telephone: (610) 902-2646

Marked Up Copy of Amended Claims

24. The method of Claim [1] 23 wherein the extended release formulation is encapsulated.

25. The method of Claim [1] 23 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose.

Please add the following new claims:

--35. The method of Claim 23 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid.

36. The method of Claim 23 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid. --

Notice of Allowability

Application No.	Applicant(s)
09/950,965	SHERMAN, ET AL
Examiner	**Art Unit**
JAMES M. SPEAR	1615

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *THE AMENDMENT FILED MARCH 05, 2002*.
2. ☒ The allowed claim(s) is/are *23-36*.
3. ☐ The drawings filed on _____ are acceptable as formal drawings.
4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   *Certified copies not received: _____.
5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. _____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.
8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

1 ☐ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☐ Examiner's Statement of Reasons for Allowance
9 ☐ Other

James M. Spear

JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615